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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

MARCH, 1952

ORIGINAL ARTICLES

EVALUATION OF DIAGNOSTIC METHODS IN DISEASES OF THYROID FUNCTION, WITH PARTICULAR REFERENCE TO RADIOIODINE TRACER TESTS*

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The diagnosis of thyroid dysfunction remains an intriguing and provocative problem for the clinician principally because a variety of endocrine, neuropsychiatric, and cardiovascular disorders often masquerade as diseases of thyroid origin. It is in this group of cases, particularly, that conventional laboratory tests may give only limited aid in differential diagnosis.

Hamilton and Soley[10] first reported that the radioiodine uptake of the thyroid gland and the urinary excretion of this radioisotope could be correlated with the state of clinical function of the gland. Since then, several investigators have studied the direct clinical application of this new diagnostic tool, employing a variety of techniques. In 1949 Werner, Quimby, and Schmidt[34]

* Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

reported on a significant number of patients in whom the 24-hour uptake of radioiodine by the thyroid gland was evaluated as an aid to the clinical diagnosis of diseases of thyroid dysfunction. Werner and his colleagues made a more recent evaluation of their considerable experience with this method[32]. Keating and his co-workers[16] presented their excellent studies on a urinary excretion technique in 1947 and again in 1950,[15] comparing it with other radioiodine tracer methods. Skanse[31] in 1949 also reported a large series of cases allowing critical appraisal of the urinary excretion of I_{131} as a diagnostic test. Other investigators have described a variety of techniques utilizing the rates of urinary excretion and uptake of I_{131} by the gland, its disappearance from the blood, and the level of I_{131} tagged serum protein. More recently, Keating, Haines, Power, and Williams[15], and Myant, Pochin, and Goldie[21] suggested the employment of a thyroid iodide clearance method as a more precise and direct test of thyroid function. We should like to present here our experience with 2 methods: 1) 24-hour I_{131} uptake, and 2) 24-hour I_{131} excretion, in the first 141 patients. These tests have been modified and adapted for use in a large and active general hospital. A thyroid iodide clearance method was very recently reported from this clinic by Berson, Yalow, Sorrentino, and Roswit, in a larger series of patients[3]. The principal objective of this paper is to evaluate the contribution of the 24-hour I_{131} uptake and excretion tests as adjuncts to clinical diagnosis of thyroid dysfunction and to compare their diagnostic accuracy with those of the initial history and physical examination, the basal metabolic rate, and the serum cholesterol level. A simple and practical technique for the performance of these radioiodine tracer methods and an analysis of their limitations is described. There is included a consideration of safe dosage factors.

Clinical Material. The patients in this investigation were individuals with a variety of disease entities, the majority presenting clinical syndromes suggesting or simulating disturbances of thyroid function (Table 1).

TABLE 1.—CLINICAL MATERIAL: PRINCIPAL FINAL DIAGNOSES

1. Euthyroid Status: 100 patients	
Neuropsychiatric diseases	34
Cardiovascular diseases	34
Pulmonary diseases	18
Gastrointestinal, biliary, and pancreatic conditions	15
Nontoxic thyroid diseases	12
Orthopedic and arthritic diseases	10
Skin diseases	1
Malignant disorders, including leukemia	8
Diabetes mellitus	8
Pituitary disorders	3
Myasthenia gravis	3
2. Hyperthyroid Status: 37 patients	
Diffuse toxic goiter	35
Toxic adenoma	3
Pituitary adenoma and acromegaly	1
3. Hypothyroid Status: 4 patients	
Myxedema, post-thyroidectomy	1
Hypothyroidism, with hypertensive and arteriosclerotic heart disease	1
Adult myxedema and hypercarotinemia	1
Hypothyroidism (cause undetermined)	1

Five diagnostic methods were employed: 1) initial history and physical examination, 2) basal metabolic rate, 3) serum cholesterol level, 4) radioiodine uptake by the gland at 24 hours, and 5) radioiodine urinary excretion level at 24 hours. There were included in this study only those patients in whom the true status of thyroid function could be finally and unequivocally established on the basis of all the cumulative evidence. A total of 141 patients fulfilled these criteria. They included 100 patients in the euthyroid state, 37 hyperthyroid, and 4 hypothyroid individuals.

Excluded from this investigation were those patients in the following categories: a) pa-

tients who received iodine-containing preparations in the course of cholecystography, pyelography, bronchography, or angiography, b) individuals who had received antithyroid drugs within 1 to 3 weeks before radioiodine tracer studies.

AGE. In Table 2 it will be noted that the age limits and average age of patients in each group (euthyroid, hyperthyroid, hypothyroid) are approximately the same. The age factor must be given consideration because it has been shown that after the age of 40 years basal heat production tends to decrease[1,2,4,5]. In addition, Bruger and Rosenkrantz[6] have shown that the incidence of hypometabolism in subjects 55 years of age or older is greater for those exhibiting arteriosclerosis than for those without this complication in the same age group.

Serum cholesterol levels were determined by the Sperry–Schoenheimer technique[30] with a range from 150 to 250 mg. per 100 cc. for normal individuals.

The radioiodine tracer tests were performed by the Radioisotope Unit in the following manner: The radioiodine (I_{131}) was received from Oak Ridge carrier-free in the form of KI in slightly basic solution. The material was standardized using Geiger counters which had been previously calibrated in terms of the "New York millicurie". Doses of 50 to 100 microcuries (mcc.) of I_{131} were employed.

Routinely there were 2 types of Geiger counter systems used for standardization of administered doses and for measurement of urine samples. Both counters were tetramethyl lead-filled thin-walled silver cathode Geiger tubes mounted inside a 1-inch thick lead

TABLE 2.—CLINICAL MATERIAL: AGE AND SEX OF PATIENTS

	Age (in years)		*Sex*		
Final status	*Average*	*Range*	*M*	*F*	*No. of cases*
1. Euthyroid	42	21–69	95	5	100
2. Hyperthyroid	40	21–61	36	1	37
3. Hypothyroid	46	28–62	4	0	4
Total			135	6	141

SEX. The scarcity of female patients in our clinical material is accounted for by the predominantly male character of the veteran population. Among the hyperthyroid subjects there were 36 males and 1 female; among the euthyroid subjects were 95 males and 5 females. The 4 hypothyroid subjects were all males. Quimby, Werner and Schmidt[26] have found no clinically significant effect of the age, sex, and season of the year upon the 24-hour uptake of radioiodine.

Methods. The history and physical examination were performed and recorded by a resident internist of the Medical Service and reviewed by a staff internist collaborating with the Radioisotope Unit, without reference to laboratory tests, including the results of I_{131} studies.

The basal metabolic rate was ascertained by a modified Roth–Benedict technique[29]. In this hospital a range of ± 15 is generally accepted as suggesting normal basal metabolic studies. However, all determinations are evaluated by the clinician in the light of the entire clinical picture and other related laboratory data.

shield. Counter 1 was mounted horizontally. A sample pan containing 5 cc. of either urine or standard solution could be placed under the counter. The sensitivity of this arrangement was 2200 counts/minute/mcc. of I_{131}. Counter 2 was mounted vertically. Samples of urine or standards up to 100 cc. were placed in a Marinelli beaker which slipped over the counter in a fixed position. The sensitivity of this arrangement was 479 counts/minute/mcc. of I_{131}.

For determination of the activity in the thyroid a Geiger counter similar to the ones discussed above was mounted in a portable lead mount with ¾-inch lead wall thickness with an open window 2¾ inches long by ¾ inch wide. This apparatus was similar to that described by Werner and Quimby[33]. A plumb-bob was dropped from a plastic holder just under the center of the open window of the counter. The over-all length of the cord and plumb-bob was 13 cm. The frame was adjusted until the bottom of the plumb-bob just touched the skin at a point on the neck above the isthmus of the thyroid gland. The sensitivity of this arrangement was 13.6

counts/minute/mcc. of I_{131} as determined from measurements made on a phantom neck. The phantom was a 1000 cc. paraffin-filled beaker whose circumference is approximately the same as an average neck. Two ½-oz. bottles filled with radioiodine were placed in the "neck" to simulate the thyroid.

Initially 100 mcc. doses were routinely employed in this study. After the first 100 cases this dose was reduced to 50 mcc. All doses of I_{131} were made up in water without additional carrier and administered orally. Whenever possible, thyroid uptake measurements were made at about 3, 6, 24, 48, and 72 hours and at weekly intervals thereafter as long as the patient retained at least 5 mcc. A 24-hour point was finally selected for assaying thyroid function because at this time 90% of the dose has been removed by the thyroid and kidneys, according to unpublished data from this clinic. Except in a few instances of toxicity, the output of organically bound iodine was not so great as to reduce significantly the amount of radioiodine in the gland. In actual practice only 2 visits by the patient are necessary, initially to ingest the dose, and 24 hours later for tracer studies over the gland.

The thyroid uptake readings are subject to at least 3 errors: 1) the statistical error introduced by the low counting rate and short time of measurement, 2) the error involved in the patient's motion during the 8-minute counting interval, and 3) the error introduced by insufficient knowledge of the exact geometry of the thyroid. Lateral motion of the patient does not contribute a significant error compared to the other factors. These errors may amount to as much as ±10%. A systematic error introduced by an error in the determination of the thyroid calibration would affect all uptake values by the same percentage. The range of uptake values associated with the various clinical states could be reliably established for a single laboratory. However, errors of this type result in differences in ranges reported from various laboratories the values of which are therefore not directly comparable[14,33].

As experience was gathered in the course of the investigation, it appears that 97% of our euthyroid individuals fell within limits of 10 to 50% uptake at the 24-hour interval. However, since an error of ±10% of the true values is accepted for *in vivo* counting, limits of uptake from 11 to 45% of the administered dose were accepted as normal in this laboratory. Patients with thyroid uptake values of 9 to 11% and 45 to 55% were reported as "borderline". An uptake of I_{131} of over 55% was always reported as definitely in the toxic range.

In urine determinations, the precision with which a determination can be made on complete samples of the first 24-hour urine is about ±3%. However, serious errors in the urine measurements are usually introduced by incomplete collections, in spite of the careful instruction given the patients, most of whom were hospitalized. In 21.3% of the cases, the collections were known to be incomplete. Thus, readings in only 111 patients were evaluated in this study. Excretion levels from 40 to 80% of the administered dose came to be accepted in our laboratory as representing normal thyroid function, because all of the true euthyroid individuals came within this range. Those with an excretion level below 40% were considered as hyperthyroids, while those above 80% were reported as hypothyroid. In general, reports to the clinical services were made on the basis of both I_{131} uptake and excretion determination. For example, patients were reported as hyperthyroid only if the uptake was greater than 55% and the excretion below 40%.

Results. A final determination was made of the diagnostic accuracy of each method of evaluation of thyroid function in each functional group (euthyroid, hyperthyroid, hypothyroid). This determination was based on final comparison with a fully established and unequivocal final diagnosis. In the hyperthyroids and hypothyroids, the final diagnosis was confirmed by surgical findings or response to medical treatment, or both. In the euthyroid group, the final diagnosis was obviously influenced by all of the diagnostic tests considered in this study. The number of hypothyroid patients is too small for statistical interpretation.

History and Physical Examination. The initial diagnosis, established on the basis of the history and physical examination alone without reference to any of the laboratory tests which followed, was compared with the final diagnosis. On this basis, 94% of the hyperthyroid patients were accurately

reported, while 6% were incorrectly designated as euthyroid. In the hypothyroid group, each of the 4 patients was properly diagnosed. However, the initial history and physical findings were less accurate in the group of euthyroid patients who were referred to the Radioisotope Unit because they represented diagnostic problems. In this group, 83% were correctly classified as euthyroid, while 16% were reported as hyperthyroid and 1% as hypothyroid. The technical error in clinical reporting of this type is obviously a function of the clinical acumen of the physician in this group of diseases, and is therefore not subject to determination of experimental error in per cent.

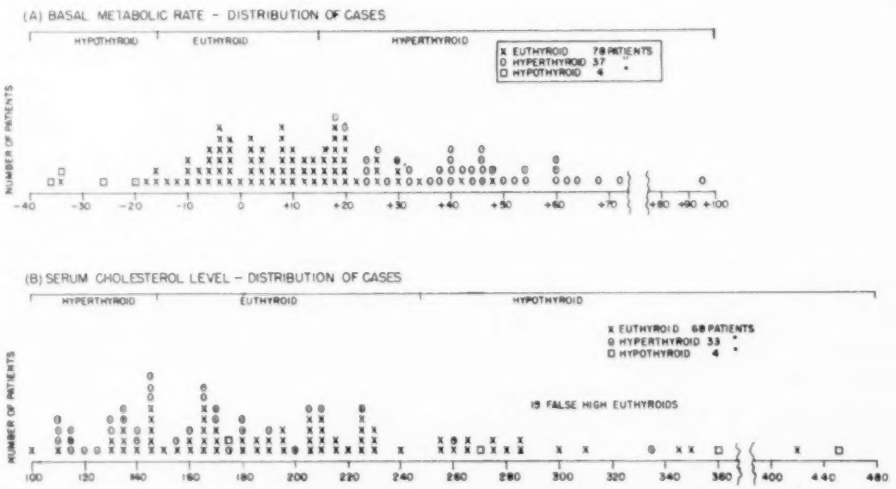
(A) BASAL METABOLIC RATE - DISTRIBUTION OF CASES
HYPOTHYROID
EUTHYROID
HYPERTHYROID
X EUTHYROID 78 PATIENTS
O HYPERTHYROID 37 "
□ HYPOTHYROID 4 "
NUMBER OF PATIENTS
-40 -30 -20 -10 0 +10 +20 +30 +40 +50 +60 +70 +80 +90 +100
(B) SERUM CHOLESTEROL LEVEL - DISTRIBUTION OF CASES
HYPERTHYROID
EUTHYROID
HYPOTHYROID
X EUTHYROID 68 PATIENTS
O HYPERTHYROID 33 "
□ HYPOTHYROID 4 "
15 FALSE HIGH EUTHYROIDS
NUMBER OF PATIENTS
100 120 140 160 180 200 220 240 260 280 300 320 340 360 400 440 480

FIG. 1.—Chart illustrating distribution of cases, basal metabolic levels, and serum cholesterol levels.

BASAL METABOLIC RATE. It may be noted from the distribution chart (Fig. 1A) that our true hyperthyroid patients all had basal metabolic rates ranging from + 18 to + 94, and these were accurately reported on the basis of an accepted range for normals of ±15. However, in our euthyroid group, in which dependable laboratory aids are most essential, it was observed that in 31% there were false high readings well up in the hyperthyroid range, and 5% were inaccurately designated as hypothyroid, with readings below −15. However, if one were to report as normal readings from −20 to +20 in this clinic, then about 20% of the euthyroid patients would fall outside this range. On the other hand, if our distribution of basal metabolic rate readings were checked against the limits of ±10%, usually accepted as normal in many clinics, then one would find that 38% of the euthyroids would have been falsely reported in the hyperactive thyroid range and 8% in the hypothyroid range.

SERUM CHOLESTEROL LEVEL. There is observed a chaotic pattern of serum cholesterol readings in the distribution chart (Fig. 1, B), which suggests at once their unreliability in the diagnosis of thyroid malfunction. Only 51% of the hyperthyroid group were correctly interpreted by this test. Of the remainder, 42% were found to have read-

ings above 150 mg. per 100 cc., while 7% were above 250 mg., well up in the hypothyroid range. In the true euthyroid group, only 59% were found to have normal serum cholesterol determinations. Of the remainder, 19% were below 150 mg. per 100 cc. and 22% above 250 mg. Three of the 4 true hypothyroid individuals were found to have readings at levels of 271, 360, and 450 mg. per 100 cc., respectively.

Of the 100 true euthyroid individuals, 97% were found in a range of 10 to 50%. However, only 89% were reported as normals, since their determinations fell between 11 and 45%. In the "borderline" or equivocal range, there were 8 normal individuals with uptakes from 45 to 55%, and 1 from 9 to 11%. In the hyperactive range were 2 normal individuals with uptakes of 66% and 68%, respectively. On this ba-

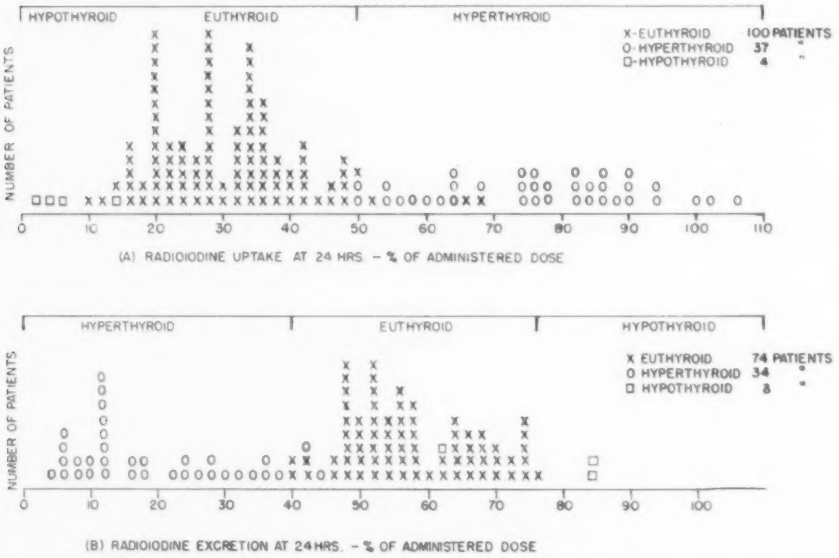
HYPOTHYROID
EUTHYROID
HYPERTHYROID
X-EUTHYROID 100 PATIENTS
O-HYPERTHYROID 37 "
□-HYPOTHYROID 4 "
NUMBER OF PATIENTS
0 10 20 30 40 50 60 70 80 90 100 110
(A) RADIOIODINE UPTAKE AT 24 HRS. - % OF ADMINISTERED DOSE
HYPERTHYROID
EUTHYROID
HYPOTHYROID
X EUTHYROID 74 PATIENTS
O HYPERTHYROID 34 "
□ HYPOTHYROID 8 "
NUMBER OF PATIENTS
0 10 20 30 40 50 60 70 80 90 100
(B) RADIOIODINE EXCRETION AT 24 HRS. - % OF ADMINISTERED DOSE

FIG. 2.—Chart illustrating distribution of cases in which radioiodine tracer tests were made.

TWENTY-FOUR-HOUR I_{131} UPTAKE BY THE THYROID GLAND. The pattern of distribution of I_{131} uptake values (Fig. 2,A), reveals no hyperthyroid patients with a 24-hour uptake of less than 50% of the administered dose. However, in recognition of the experimental error of $\pm 10\%$, 4 patients (10.8%) were reported as borderline or equivocal because their uptake readings fell below 55%. On this basis, 89% of the hyperthyroid patients were correctly reported. The average uptake was approximately 77%.

sis, 89% of the euthyroid patients were correctly diagnosed by the 24-hour I_{131} uptake method.

Of the 4 hypothyroid patients, 3 had uptakes well below 10%, while one was reported at 14%.

TWENTY-FOUR-HOUR I_{131} URINARY EXCRETION. Of the 34 hyperthyroid patients studied by this method, only 2 fell in the euthyroid range (40 to 80%). Thus, a diagnostic accuracy of 94% was attained in this group. It was found that in the 74 euthyroid cases where urinary collection was believed to be

complete, the measurements of 24-hour I_{131} excretion all fell between 40 and 80%. However, 2.7% of these patients had determinations which fell in the borderline range and were reported as equivocal. The excretion level of one of the hypothyroids was found to be in the euthyroid range.

Discussion. It is generally agreed that frank toxic hyperthyroidism is recognizable clinically with relative ease. This was affirmed by the results of our investigation. However, in the milder variants of this disease, especially in borderline cases, the clinician must rely considerably upon adjunct laboratory aids. The problem of differential diagnosis is further complicated by euthyroid individuals with certain disease entities which simulate disorders of thyroid function. Most of these problems are neuropsychiatric, cardiovascular, and endocrine in origin. Of 100 such patients in our series, 16 were incorrectly considered hyperthyroid on the basis of the initial history and physical examination alone, without reference to laboratory tests. The need for reliable diagnostic laboratory aids in this group is obvious.

Although the basal metabolic rate is widely employed as a screening test in problems such as these, in our experience this test has proved of doubtful value in the borderline cases. Of our euthyroid individuals, 36% had abnormally high or low basal metabolic rate values, on the basis of our accepted normal range of ±15%. The limited accuracy of this procedure has been further emphasized by Roth and Roth[29] because of the special requirements of the apparatus, the patient, and the physician. We have found the basal metabolic rate particularly unsuited for individuals with severe neuropsychiatric disease, cardiac decompensation and asthma. In such patients, the basal state is difficult to approach, and one cannot depend upon the patients' cooperation. At best, the basal metabolic rate is only an indirect index of thyroid function. That it is an insensitive test as well is demonstrated by the fact that both hyper- and hypothyroid individuals may be found in the range of ±20. Even if the normal range were extended to ±20, as many as 20% of our euthyroid patients would fall above and below these levels.

It has been further demonstrated by Mountain *et al.*[20] and Rosenkantz and Marshall[27] that hypertensive vascular disease is responsible for a significant incidence of hypermetabolism; also patients with cardiac strain or failure[9,22-24], pulmonary disease[7], elevated temperature, leukemia, and Hodgkin's disease may have a basal metabolic rate which is elevated to abnormal levels.

In our experience it has not been unusual to find evidence of hypermetabolism among neuropsychiatric patients, particularly those in hysterical or anxiety states, with hyperventilation. Roth and Buckingham[28] long ago called attention to the effect which changes in the mid-position of the chest had upon the slope of the spirogram. Very recently Williard and Wolf[35] also reported that a change in chest volume may produce either a falsely low or a falsely high apparent metabolic rate, using the Benedict–Roth closed circuit apparatus. A change in chest volume may occur with apprehension, mild pain, and dyspnea. In addition, there may be oxygen loss because of mechanical difficulties or perforated eardrums, or in the aerophagics. It is therefore apparent that there are many factors which may produce extrathyroidal hypermetabolic readings. Jaffe and Ottoman recently reported a diagnostic error of 32.7% in their basal metabolic tests[14]. Werner and his colleagues[32] found approxi-

mately 50% of basal metabolic readings beyond the usually accepted limits of ±10%, and expect to substitute the radioiodine tracer technique (24-hour uptake) for the basal metabolic determination as the initial routine laboratory screening procedure in the diagnosis of thyroid disorders. We are in agreement with this viewpoint.

It has been generally held that in hyperthyroidism, serum cholesterol levels are low, while hypercholesterolemia is associated with hypothyroidism[8,13,17,19]. Although Hurxthal states that the serum cholesterol level is superior to the basal metabolic rate [11-13], many other investigators believe that this test cannot be correlated with other objective measures of thyroid activity[8,17,19]. We are entirely in agreement with the latter. In our study, about 40% of the euthyroid patients and more than half of the hyperthyroids were falsely reported by the serum cholesterol determinations.

The 24-hour I_{131} uptake and excretion tests employed in this investigation as part of a more extended study have been very helpful indeed in differential diagnosis involving problems of thyroid malfunction. In actual practice in our clinic they have proved far superior to the basal metabolic rate and serum cholesterol determinations. They are safe, rapid, and convenient, requiring no unusual preparation, and can be performed at any time of the day. Of the greatest importance is the fact that, in the uptake study at least, the cooperation of the patient is not required. In the conduct of the urinary excretion method, the collection or urine samples may present considerable difficulty. However, when the urine collection is complete, this method for assaying thyroid function may be somewhat more accurate than the uptake study. It is certainly technically easier to measure the urine instead of the patient. In critically ill or otherwise uncooperative individuals, urine samples may be collected, *in toto*, by catheterization. In addition, tracer doses as low as 10 mcc. can probably be employed in the excretion technique, thus adding greatly to the safety factor.

Despite their obvious advantages over the basal metabolic rate and cholesterol determinations as laboratory aids to the clinician, the 24-hour I_{131} uptake and tracer methods suffer from the same disadvantages as other present available radioiodine tracer techniques, namely, overlap of euthyroid and hyperthyroid subjects. Perfection of these particular tracer techniques and others available at present cannot eliminate a persistent overlap, because each of these tests measures only the competition between the kidneys and thyroid for the circulating iodide. This overlap is not necessarily due to biological variations in thyroid function but rather to the indirect and relative nature of the conventional diagnostic laboratory tests. Keating, Haines, Power, and Williams[15] predicted that it appeared unlikely that the accumulation of a large series of normal values would improve the diagnostic efficiency of presently available radioiodine tests to any significant extent. Actually, the study of Werner and his associates in September, 1950, on 1000 normal individuals and 400 abnormals, fulfills this prediction[32]. Werner and his group found as many as 20% of euthyroids outside their accepted normal range.

It appears to us that further improvement in diagnostic accuracy employing radioiodine tracer methods is to be achieved, not by refining the precision of present available methods, but by further study of thyroid iodide clearance. Such a prediction has also been made by Keating, Haines, Power, and Williams[15], and Myant, Pochin and

Goldie[21]. The thyroidal plasma I_{131} clearance rates, representing a direct measurement of the iodine accumulating function of the thyroid and being independent of extraneous factors such as renal function, have successfully reduced the overlap of the euthyroid and hyperthyroid subjects[3].

It may be well to consider at this point the question of possible impairment of physiological function of the thyroid gland from cumulative doses of repeated radioiodine tracer tests. Marinelli, Quimby, and Hine[18], assuming uniform concentration of the isotope, calculated that 1 mcc. of I_{131} destroyed, per gram of gland tissue, will deliver approximately 158 equivalent roentgens (e.r.) to the thyroid. Thus, our hyperthyroid patients, with a mean or average uptake of 77% and gland size averaging about 50 gm., would receive 120 e.r. to the thyroid gland, after a 50-mcc. test dose. Our euthyroid individuals, with a mean uptake of 31% and assuming a gland size of about 25 gm., would receive even less: approximately 100 e.r. with each test dose. The hypothyroid subjects would receive about 35 e.r.

One of the Authors (B.R.) has delivered tissue doses of 6000 roentgens (r.) in 30 to 60 days to several hundred patients with head and neck neoplasms in the past 15 years, employing deep Roentgen-ray therapy. The normal thyroid gland in the path of the Roentgen-ray beam received the full impact of this dose of irradiation, yet no immediate or delayed impairment of thyroid function was clinically observed. Nor was there later discovered evidence of thyroid carcinoma in those patients who survived their primary malignant disease. If a safety factor of 10 may be assumed for the tracer test, then on the basis of this experience, 600 r may serve as a guide to the maximum permissible cumulative dose to the thyroid gland, as far as function and neoplastic change are concerned.

Following questionnaires submitted to 101 radiologists and thyroid specialists, Quimby and Werner[25] concluded that late malignant changes following Roentgen radiation to the thyroid gland, if they do exist, are very rare indeed.

Some consideration must be given to the observation that when I_{131} is used for hyperthyroid therapy, larger radiation doses expressed in equivalent roentgens are required to produce the same physiological effect as that obtained from Roentgen rays. This may be due to the spotty distribution of I_{131} in the gland resulting in non-uniform irradiation. Under these circumstances, some parts of the thyroid gland receive an amount greatly in excess of the estimated radiation dose, which is based on the assumption of uniform concentration. Every effort should therefore be made to reduce the size of the dose.

The size of the tracer dose and the frequency with which it can be repeated is obviously limited by a consideration of the maximum dose which can safely be delivered to the thyroid gland, since the generalized body radiation from a typical tracer dose is less than the recommended safe levels permitted radiation workers.

Summary 1. We have presented an evaluation of 2 radioiodine tracer techniques; 1) 24-hour I_{131} uptake, and 2) 24-hour I_{131} excretion, as aids to the clinician in the diagnosis and differential diagnosis of diseases of thyroid malfunction in a series of 141 patients.

2. The potentialities and limitations of these 2 radioiodine tracer methods have been discussed. Their diagnostic accuracy has been compared with that of the initial history and physical ex-

amination, and of conventional laboratory aids, including the basal metabolic rate and the serum cholesterol level.

3. Although the 24-hour I_{131} uptake and excretion tests have been shown to be of invaluable aid to the clinician, and far superior to the basal metabolic rate and serum cholesterol determinations, there still remains an irreducible overlap between euthyroid and hyperthyroid subjects. This overlap appears to be due to extraneous factors and not to biological variations in function of the thyroid gland.

4. There still remains a pressing need for a diagnostic method which will represent a direct measurement of the iodine accumulating function of the thyroid, independent of extraneous factors such as renal function, and thus reduce the overlap of the euthyroid and hyperthyroid subjects. The thyroid iodine clearance method promises to circumvent these difficulties.

5. A consideration of safe dosage factors has been included.

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THE EFFECT OF ANTIHISTAMINES ON THE PAIN THRESHOLD: DOLORIMETER STUDIES ON PYRIBENZAMINE AND ANTISTINE*

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A marked interrelationship has been established clinically and pharmacologically between antihistaminic and local anesthetic therapeutic agents. This association has been highlighted especially by the satisfactory analgesic[1,8,12,15-19,21,33] and antihistaminic[2,9-11,37,39,40] effects obtained following the administration of intravenous procaine.

Antihistaminics, which are known to be rapidly and well absorbed from the gastrointestinal tract, have been found to have potent local anesthetic activity[4,6,7,13,22,29,32,34-36] equal or superior to that of procaine at equivalent concentrations[13].

Graubard[14] postulated that intravenous procaine may possibly relieve pain resulting from injury by abolishing reflex arcs initiated by trauma and resulting in local capillary dysfunction. He suggests that the unusual analgesic effectiveness of intravenous procaine may possibly be explained by a local concentration of procaine at a site of tissue trauma as great as 8 times that found in the normal body tissues at the same time. A similar analgesic activity resulting from an equivalent concentration of an antihistaminic working also as a local anesthetic might also occur in areas of trauma.

The maximum beneficial effects of intravenous procaine hydrochloride have usually been obtained by using a 0.1% solution in a dosage unit which totals 4 mg./Kg. of body weight[20]. A unit is delivered over a period of 20 minutes. This weak concentration of procaine is diluted still further by the total blood volume and the tissue fluids. Since intravenous procaine seems to exert its analgesic action at such an extremely low drug concentration, following relatively small dosages, and over unusually long periods of time, it was thought that antihistaminic agents with local anesthetic activity might have a similar analgesic activity.

It was therefore decided to investigate the possibility that the antihistaminic agents Pyribenzamine (N′-pyridil-N′-benzyl-N-dimethyl-ethylene diamine monohydrochloride) and Antistine (2-phenyl-benzylaminomethyl-imidazoline hydrochloride) might have properties capable of raising the pain threshold of the intact and/or traumatized skin.

Methods. The Hardy-Wolff-Goodell pain apparatus utilized in this study and the technique of its application were first described in 1940[24-26] and have been used frequently since that time in studying analgesic agents[3,27,28,30,31,41]. The pain threshold of the in-

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dividual is obtained by focusing the radiant energy of a 500-watt projection bulb through a solenoid shutter (regulated electronically to open for 3 seconds) onto the skin which has been previously blackened with India ink to assure complete and uniform absorption of radiation.

Cutaneous pain thresholds are measured in response to controlled radiant heat stimuli and are expressed by the number of mcal (millicalories per second per square centimeter of exposed skin) required to provoke a sensation of heat finally "rising" or "swelling" to a distinct sharp stab or prick of pain at the end of the 3-second exposure. In the Hardy-Wolff-Goodell dol scale of pain intensity, 14 mcal (1 dol) represents the first 2 of 21 discriminable steps between the pain threshold and the maximum (ceiling) intensity of pain[25,26]. Since only under ideal experimental conditions are trained subjects able to discern this many steps in pain intensity between the pain threshold and ceiling, there are usually only 10½ readily identifiable division (dols) in the Hardy-Wolff-Goodell dol scale of pain intensity[25,26]. The limit of the ability of trained subjects to discriminate differences in intensity of pain stimuli near the pain threshold is about 5 mcal[23].

The 18 subjects employed in this study, 3 men and 15 women, aged 16 to 51, were trained in both the procedure of the Hardy-Wolff-Goodell technique and the experience of the pain threshold sensation. Subjects were tested on the dorsum of the hand. Tests were begun approximately 1 hour after breakfast. Each subject was observed over a 3 to 4-hour period following the administration of both the experimental and control tablets. During this period no activity was allowed and extraneous stimuli were reduced to a minimum. Tests were carried out uniformly in a comfortable position and at a comfortable room temperature. Subjects were not aware of the implications of their responses to these tests.

PART 1. THE EFFECT OF ANTIHISTAMINIC AGENTS PYRIBENZAMINE AND ANTISTINE ON THE PAIN THRESHOLD OF THE INTACT SKIN. *Group 1.* The pain thresholds of 10 trained subjects who were to act as controls for this study were determined before and 15, 30, 60, 90, 120, 150, 180, 210, and 240 minutes following the ingestion of a placebo tablet.*

Group 2. The pain thresholds of the 15 trained subjects who comprised the Pyribenzamine experimental group were similarly determined before and 15, 30, 60, 90, 120, 150, 180, 210, and 240 minutes following the ingestion of a 50-mg. tablet of Pyribenzamine.

Group 3. The pain threshold of the 8 trained subjects who comprised the Antistine experimental group were similarly determined before and 15, 30, 60, 90, 120, 150, 180, 210, and 240 minutes following the ingestion of a 100-mg. tablet of Antistine.

PART 2. THE EFFECT OF THE ANTIHISTAMINIC AGENT PYRIBENZAMINE ON THE PAIN THRESHOLD OF TRAUMATIZED SKIN. A rectangular area of skin 2 inches by 3 inches on the forearm of each of 5 trained subjects was uniformly exposed to ultraviolet radiation for a period calculated to produce an area of maximum erythema just short of vesiculation. The subjects were dismissed for 24 hours. At the end of this time the irradiated areas were so sensitive to radiant heat that it was necessary to modify the Hardy-Wolff-Goodell technique by decreasing the skin exposure time from 3 seconds to 2 seconds in order to obtain pain threshold readings above the lowest dial reading of 100 mc.

The pain threshold of the traumatized area was carefully determined 4 times.† The 0 minute reading is therefore an average of these 4 pain threshold determinations. A 50-mg. tablet of Pyribenzamine was then administered to each of the 5 subjects and their pain thresholds were studied at intervals of 30 minutes for the next 4 hours (Table 4.)

Results. The pain thresholds recorded in this study are reproduced and summarized in Tables 1, 2, 3, and 4.

Part 1. The data in Tables 1, 2, and 3 were subjected to separate analyses of variance[5]. For the placebo control group, it was found that individuals differ significantly from each other in their pain thresholds, as might readily

* The placebo tablet, supplied by the Ciba Pharmaceutical Products, Inc., was identical to the Pyribenzamine tablet commercially available except for the substitution of inert filler for the active ingredient, Pyribenzamine hydrochloride.

† In addition to obtaining the required initial pain threshold, 3 additional determinations were also made to be certain that the radiant heat incident to the test procedures did not further traumatize the area, thereby decreasing the pain threshold. This was not found to occur.

TABLE 1.—PAIN THRESHOLDS (MCAL) OF 10 PATIENTS TAKING CONTROL TABLETS

Patient's No.	*Time in Minutes After Taking Tablet*										*Individual Average*
	0	*15*	*30*	*60*	*90*	*120*	*150*	*180*	*210*	*240*	
1	203	206	198	202	205	208	204	206	209	205	204.6
2	195	199	202	206	203	190	193	201	204	198	199.1
3	210	213	216	216	216	218	209	217	213	213	214.1
4	235	232	236	236	233	228	242	239	228	228	233.7
5	247	247	244	246	256	238	234	238	243	241	243.4
6	207	203	211	201	193	204	207	212	209	204	205.1
7	200	205	208	204	204	194	196	196	205	204	201.6
8	205	202	202	199	208	204	202	202	213	210	204.7
9	194	186	191	188	186	197	194	205	196	196	193.3
10	207	207	203	199	199	193	194	202	202	196	200.2
Period average	210.3	210	211.1	209.7	210.3	207.4	207.5	211.8	212.2	209.5	

TABLE 2.—PAIN THRESHOLDS (MCAL) OF 15 PATIENTS TAKING 50 MG. OF PYRIBENZAMINE

Patient's No.	*Time in Minutes After Taking Medication*										*Individual Average*
	0	*15*	*30*	*60*	*90*	*120*	*150*	*180*	*210*	*240*	
1	205	208	215	203	205	208	202	196	204	207	204.9
2	200	207	209	207	210	213	207	210	206	208	207.7
3	220	223	232	228	231	228	225	218	215	215	223.5
4	240	243	235	242	251	248	244	237	244	247	243.1
5	255	258	263	260	257	265	272	262	265	262	261.9
6	212	209	204	213	211	208	206	203	205	207	207.8
7	205	207	210	213	220	218	209	205	209	198	209.4
8	207	203	212	214	205	200	204	208	211	213	207.7
9	198	202	202	211	211	214	211	214	211	192	206.6
10	215	218	221	227	233	223	223	223	227	222	223.2
11	190	187	195	197	199	196	205	198	195	195	195.7
12	215	215	211	211	208	204	207	213	210	208	210.2
13	195	202	197	199	191	188	191	194	203	188	194.8
14	217	213	213	213	223	219	215	221	212	216	216.2
15	191	194	196	187	189	202	198	195	195	187	193.4
Period average	211.0	212.6	214.1	215.0	216.3	215.6	214.6	213.1	214.1	211.0	

TABLE 3.—PAIN THRESHOLDS (MCAL) OF 8 PATIENTS TAKING 100 MG. OF ANTISTINE

Patient's No.	*Time in Minutes After Taking Medication*										*Individual Average*
	0	*15*	*30*	*60*	*90*	*120*	*150*	*180*	*210*	*240*	
1	208	208	204	213	209	209	205	202	199	204	206.1
2	205	198	198	201	211	214	203	200	205	200	203.4
3	214	217	221	221	221	221	218	213	213	216	217.5
4	240	235	235	245	248	254	254	243	239	235	242.8
5	255	259	254	262	266	254	254	250	244	248	254.6
6	214	221	209	209	206	203	213	209	209	204	209.7
7	205	201	206	206	203	213	217	213	213	209	208.6
10	210	205	205	205	203	203	206	209	213	220	207.9
Period average	218.9	218.0	216.5	220.2	220.9	221.4	221.2	217.4	216.9	217.0	

have been expected. (This was true for each treatment group studied.) There was no significant trend for this group in average pain thresholds at different time periods throughout the 4 hours of observation. The mean pain thresholds appear in Fig. 1.

For the 15 patients who ingested 50 mg. of Pyribenzamine it was found that the trend of mean pain thresholds throughout the 4 hours of observation was barely significant at the 5% level. It will be noted (Table 2 and Fig. 1) that the highest mean pain threshold occurred 90 minutes after ingestion of Pyribenzamine. When the mean values at 0 and 90 minutes were compared by the t-test, it was found that the difference between mean values was just about

TABLE 4.—PAIN THRESHOLDS (MCAL) OF 5 PATIENTS WHO TOOK 50 MG. OF PYRIBENZAMINE AFTER ULTRAVIOLET RADIATION OF SKIN

Patient	*Before U-V Radiation*	*After U-V Radiation Time in Minutes After Taking Medication*							*Individual Average*
		0	*30*	*60*	*90*	*120*	*150*	*180*	*210*	
A	200	115	111	113	117	124	114	110	107	113.9
B	205	115	112	109	109	106	113	117	113	111.8
C	212	125	121	121	131	128	124	124	120	124.2
D	230	105	105	103	107	111	114	114	111	108.8
E	185	125	125	130	126	123	133	136	127	128.1
Period average	206.4	117.0	114.8	115.2	118.0	118.4	119.6	120.2	115.6	

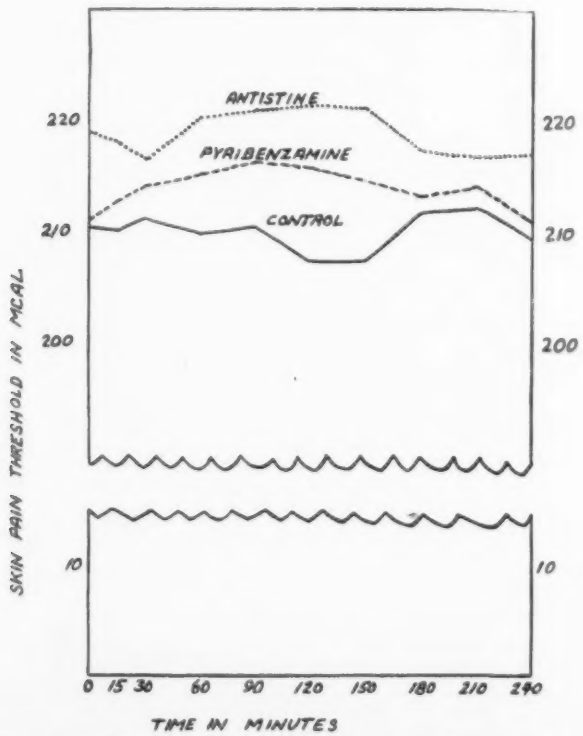

FIG. 1.—Mean pain thresholds (in mcal, or millicalories) at different time periods, before and after taking control tablet, 50 mg. of Pyribenzamine, or 100 mg. of Antistine.

significant (P 2%). The difference in mean values, 5.3 mc, must be interpreted in the light of clinical importance, however.

In the group of 8 patients who took 100 mg. of Antistine, the trend of mean pain thresholds over the 4 hours of observation (Fig. 1) was not statistically significant. When the pain thresholds of the 8 patients who took both Pyribenzamine and, later, Antistine (Tables 2 and 3) were studied by analysis of variance, it was found that there was no significant difference in the average pain thresholds with the 2 medications. Some individuals show quite a difference in one direction or the other, whereas others show practically no difference.

PART 2. The pain threshold determinations over a 3½-hour period on 5 patients whose skin had been traumatized by ultraviolet radiation, and who 24 hours later ingested 50 mg. of Pyribenzamine, appear in Table 4. Analysis of variance performed on these data discloses that there was no significant trend of mean pain thresholds over the 3½-hour period after taking Pyribenzamine.

Discussion. Kibler and Schnaper[27], using the Hardy-Wolff-Goodell technique, reported only an insignificant rise in the pain threshold following the administration of intravenous procaine. The findings described in the present paper for the 2 antihistaminic agents studied are in keeping with Kibler and Schnaper's report. The reader is referred to the discussion of results appearing in their paper[27].

Although our study has not demonstrated a material increase in the pain threshold following the administration of 2 antihistaminic preparations, this report does not presume to pass judgment upon the clinical analgesic activity of antihistaminic agents. It merely points out that quantitative increases in cutaneous pain threshold following the ingestion of Pyribenzamine and Antistine are not demonstrable with the Hardy-Wolff-Goodell technique. A similar situation appears to exist with aspirin[31,38,40].

In the case of the effect of Pyribenzamine on the pain threshold of traumatized areas, it is possible that the tissue damage was not great enough to have allowed detection of an analgestic effect. With the Hardy-Wolff-Goodell method, however, a more severe continuous spontaneous pain would invalidate the technique.

The pain threshold readings at the initial time periods for both the Pyribenzamine and Antistine groups were higher than the initial readings for the same individuals in the control group. It is believed that these consistently higher readings were possible due to some "learning effect," since the control-tablet readings were obtained in each instance before the studies on the antihistamine drugs. For this reason, no direct comparisons were made between readings of the same individual in the control and Pyribenzamine groups or the control and Antistine groups.

While statistical significance may be asserted (although not at the 1% level) in the trend of pain thresholds following the ingestion of Pyribenzamine, and between the readings at 0 and 90 minutes for this group, it must be emphasized that the average readings did not differ from one another by more than 5.3 mc. With the Hardy-Wolff-Goodell technique, such readings are clinically unimpressive, since, even with trained subjects, a numerical pain threshold raising effect of less than 7 mc (½ dol or 3%) is most difficult to determine or interpret with certainty and is of slight clinical importance.

Summary. 1. The effect of Pyribenzamine upon the cutaneous pain thresh-

old of 15 trained human subjects and the effect of Antistine upon the cutaneous pain threshold of 8 trained human subjects were studied, using the Hardy-Wolff-Goodell technique.

2. A 50-mg. dose of Pyribenzamine or a 100-mg. dose of Antistine did not materially alter the pain threshold of intact human skin.

3. A 50-mg. dose of Pyribenzamine did not materially effect the pain threshold of traumatized skin in 5 trained subjects.

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CEREBRAL PHYSIOLOGY OF THE AGED* †

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THE nitrous oxide technique introduced by Kety and Schmidt[7] for the estimation of cerebral blood flow and oxygen consumption has made possible the quantitative determination of these functions in various clinical states. In many such studies, results in persons of widely varying ages have been compared with those in young normal subjects despite the known rising incidence of subclinical cerebral vascular disease accompanying advancing age. Except for a preliminary survey[2] of cerebral physiology in the presence of the psychoses of the aged, little attention has been paid to cerebral hemodynamics and oxygen consumption in the older age groups. Earlier studies[1,16] limited to the investigation of cerebral arteriovenous oxygen differences failed to demonstrate significant variations with age. It was nevertheless recognized that simultaneous proportional changes in cerebral blood flow and metabolism which might have been present could not be detected by this method.

Method. In the present study, cerebral hemodynamics and oxygen consumption of persons below 50 years of age with no evident central nervous system disturbance (Group 1) have been compared with these functions in persons 50 years of age or older. The subjects in the older age range were further classified into the 4 following groups: Group 2, those with no evident central nervous system disturbance; Group 3, those with an old or recent cerebral vascular accident (cerebral thrombosis) but no gross psychic disturbance; Group 4, those with confusion and evidence of cerebral vascular disease; and Group 5, those with depression of consciousness (stupor to coma) resulting from cerebral vascular disease. In addition to the above comparison, the effect of the inhalation of 10% oxygen or 5% carbon dioxide on the cerebral hemodynamics and metabolism of older persons with cerebral vascular disease was also investigated.

Scheinberg and Stead's[14] modification of Kety and Schmidt's[7] procedure for the determination of cerebral blood flow (CBF) was applied in this study. The gas mixtures utilized were those described by Kety[8]. Blood oxygen was determined by the manometric technique of Van Slyke and Neill[10]. Mean arterial blood pressure (MBP) was obtained directly from the femoral artery by means of a damped anaeroid manometer. The cerebral oxygen consumption ($CMRO_2$), cerebral vascular resistance (CVR), and cerebral oxygen delivery (CDO_2) were calculated as follows: $CMRO_2$ ($cc.O_2$/min./100 gm. brain) $= \frac{CBF \times (A\text{-}V)\ O_2}{100}$, CVR (mm. Hg/cc. blood/min./100 gm. brain) $= \frac{MBP}{CBF}$; CDO_2 ($cc.O_2$/min./100 gm. brain) $= \frac{CBF \times \text{arterial } O_2}{100}$.

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Results. Table 1 presents results obtained in 10 observations of 9 individuals between the ages of 23 and 42 years with no clinical evidence of vascular or parenchymatous central nervous system disease. A number of hypertensives were, however, included in this group in order to make it more comparable to the older age groups. The mean values noted are similar to those previously reported by Kety and Schmidt[7] for normal young persons but somewhat lower than those observed by Scheinberg[14] in such subjects.

TABLE 1.—SUBJECTS BELOW AGE 50 YEARS WITH NO CENTRAL NERVOUS SYSTEM DISEASE (GROUP 1)

Age	*CBF**	*$CMRO_2$*	*CVR*	*CDO_2*	*AO_2*	*CVO_2*
23	60.1	4.0	1.7	9.7	15.97	9.29
28	72.6	4.0	1.8	11.7	16.19	10.68
30	52.4	2.9	1.8	6.7	12.79	7.18
	53.6	3.4	1.8	6.5	12.05	5.80
34	54.3	3.4	1.8	9.3	17.07	10.79
37	51.8	3.9	2.2	8.7	16.72	9.35
39	42.1	3.0	2.0	5.5	12.25	5.10
40	48.6	3.2	2.5	5.2	10.77	4.16
42	50.8	3.0	2.5	8.2	16.05	10.16
42	54.8	3.7	2.4	8.2	15.01	8.19
			Mean Values			
34	54.2	3.5	2.1	8.1	14.72	8.25

* In this and other tables, CBF signifies cerebral blood flow in cc./min./100 gm. of brain; $CMRO_2$, cerebral oxygen consumption in cc./min./100 gm. of brain; CVR, cerebral vascular resistance in mm. Hg/cc. blood/min./100 gm. of brain; CDO_2, cerebral oxygen delivery in cc./min./100 gm. of brain; AO_2, arterial oxygen content in cc. O_2/100 cc. of blood; CVO_2, cerebral venous oxygen content in cc. O_2/100 cc. of blood; MBP, mean arterial blood pressure in mm. of Hg.

Table 2 presents the results of 22 observations in 15 persons between the ages of 50 and 91 years. All of these subjects (Group 2) were alert and well oriented, and there was neither history nor clinical evidence of cerebral vascular accident or parenchymatous neurological disease. In this group, again, there were included some individuals with arterial hypertension. The mean value for cerebral blood flow is significantly ($P < .01$) lower than in the group of normal young persons. A similarly significant ($P < .001$) reduction appears also in the determination of mean cerebral oxygen consumption. The calculated value for mean cerebral vascular resistance is elevated above that value for the younger subjects because of the lower mean cerebral blood flow. Mean cerebral oxygen delivery is moderately reduced chiefly because of the reduction in mean cerebral blood flow. The above-noted decrease in mean cerebral blood flow was observed despite a minor tendency toward reduction in mean arterial and cerebral venous oxygen content, probably due to a slightly lower hemoglobin level. The smaller mean cerebral arteriovenous oxygen difference in the presence of a decreased mean cerebral

blood flow is due to a disproportionate reduction in mean cerebral oxygen consumption.

Table 3 presents the results of 15 observations in 13 persons between the ages of 50 and 78 years with old or recent cerebral thrombosis but no mental disturbances. All cerebral values excepting cerebral venous oxygen content are very significantly ($P < .001$) altered from those in the younger subjects of Group 1. The mean cerebral blood flow in this group with unquestionable evidence of cerebral vascular disease is not significantly lower than in Group. 2. The small reduction in mean cerebral oxygen consumption as compared to that of Group 2 is also of no statistical significance. The marked increase in mean cerebral vascular resistance over that of Group 2 is the result of both the slightly reduced mean cerebral blood flow and the higher mean arterial blood pressure (not tabulated) of Group 3. The absence of appreciable diminution of

TABLE 2.—SUBJECTS 50 YEARS OLD OR OVER WITH NO CENTRAL NERVOUS SYSTEM DISEASE (GROUP 2)

Age	*CBF*	*$CMRO_2$*	*CVR*	*CDO_2*	*AO_2*	*CVO_2*
50	54.8	3.2	1.3	8.2	14.98	9.08
52	51.4	3.5	1.8	7.3	14.17	7.39
55	24.7	1.9	6.5	3.9	15.68	9.67
56	62.5	3.9	2.2	8.8	12.52	8.62
57	49.2	2.7	2.4	5.4	11.05	5.42
	43.4	2.5	3.1	5.0	11.61	5.83
58	48.2	2.1	2.7	7.4	15.34	10.71
62	42.3	1.6	2.0	4.2	9.92	6.11
63	38.8	1.3	3.5	3.2	8.07	4.76
72	41.1	1.9	3.2	4.9	12.03	7.31
	42.7	1.8	2.5	4.8	11.29	7.05
77	27.8	1.4	4.0	4.3	15.31	10.42
78	34.9	2.9	2.9	5.7	16.41	8.21
	37.0	2.1	2.3	5.6	15.12	9.36
	34.2	2.1	2.6	5.1	14.78	8.75
	32.0	2.3	2.7	4.9	15.25	9.98
79	57.9	3.1	1.9	7.3	12.58	7.31
81	34.7	3.0	4.4	4.3	12.49	3.79
86	30.6	2.0	2.7	4.3	13.88	7.33
91	36.1	2.2	2.6	6.1	16.88	10.80
	42.4	2.6	2.1	6.2	14.63	8.43
	44.1	2.3	2.0	6.3	14.29	9.20
			Mean Values			
68	42.5	2.4	2.9	5.7	13.24	7.77

See Table 1 for explanation of abbreviations.

mean cerebral oxygen delivery, in spite of the slightly reduced mean cerebral blood flow, is attributable to the similarly small (not statistically significant) increase in mean arterial oxygen content over that of Group 2. The mean cerebral venous oxygen content is increased by the same extent, probably because of the same factors mental status ranging from slight confusion to complete disorientation. The values for this group in most respects are not significantly different from those in Groups II and III and differ therefore from those of Group I to a similar extent.

In Table 5 are recorded the results of 14 observations in 13 subjects be-

TABLE 3.—SUBJECTS 50 YEARS OLD OR OVER WITH OLD OR RECENT CEREBRAL VASCULAR ACCIDENT, BUT NORMAL MENTAL STATUS (GROUP 3)

Age	*CBF*	$CMRO_2$	*CVR*	CDO_2	AO_2	CVO_2
50	60.7	1.3	2.8	8.8	14.56	12.31
50	37.5	2.1	4.5	6.3	16.86	11.26
	36.0	2.0	5.0	6.0	16.71	11.15
53	26.1	2.7	5.4	4.9	18.59	8.44
53	29.2	2.1	3.5	4.0	13.34	6.44
54	32.6	1.6	3.3	3.9	12.05	7.09
65	29.8	1.6	3.6	4.4	14.67	9.42
66	31.9	2.8	3.9	6.0	18.71	9.93
	39.0	3.5	2.9	6.9	17.78	8.81
67	25.7	1.0	5.8	4.4	17.03	13.03
70	32.5	2.2	4.2	4.0	12.33	5.69
70	34.8	1.0	4.2	4.2	12.15	9.24
71	32.6	3.3	2.7	7.0	13.25	7.00
75	36.5	2.6	2.7	6.2	16.85	9.64
78	40.7	3.2	2.3	6.4	15.69	7.70
			Mean Values			
63	36.4	2.2	3.8	5.5	15.04	8.97

See Table 1 for explanation of abbreviations.

(chiefly the higher hemoglobin level) with the result that the mean cerebral arteriovenous oxygen difference is practically unchanged.

Table 4 is composed of 20 observations in 18 individuals between the ages of 53 and 92 years. All of these subjects had evidence of peripheral arteriosclerosis and/or arterial hypertension and exhibited an abnormal tween the ages of 50 and 80 years. All of these individuals had evidence of peripheral arteriosclerosis, arterial hypertension, or a combination of both. All the subjects exhibited a disturbance of consciousness ranging from stupor to deep coma. The mean cerebral values do not differ significantly from those of Groups 2, 3, and 4. The mean arterial and cerebral venous oxygen

contents are slightly higher (possibly because of dehydration in the comatose patients.)

When Groups 3, 4, and 5 are considered collectively to include "subjects over age 50 with cerebral vascular disease" and as such compared with Group 2, the difference in mean cerebral blood flow becomes significant ($P < .05$.) However, the mean cerebral oxygen consumption of the combined group still is not significantly different from that of Group 2.

In Table 6 are presented the results of 8 experiments in which, immediately after control determinations, patients between the ages of 63 and 81 years breathed an atmosphere containing 10% oxygen for an interval of ½ hour; the cerebral blood flow and oxygen consumption were again determined during the final 10 minutes of this period. Although the cerebral blood flow showed a small to moderate increase in every case and the mean, therefore, also increased moderately,

TABLE 4.—SUBJECTS 50 YEARS OLD OR OVER WITH VASCULAR DISEASE AND MENTAL CHANGES (GROUP 4)

Age	*CBF*	*$CMRO_2$*	*CVR*	*CDO_2*	*AO_2*	*CVO_2*
53	21.4	1.0	5.5	3.2	15.12	10.07
56	30.0	2.4	4.9	5.5	17.68	9.56
57	57.9	2.4	1.7	4.3	7.34	3.19
	54.9	2.1	1.6	3.7	7.06	3.17
	51.4	2.3	1.9	3.8	7.47	2.95
63	36.4	2.1	2.9	6.7	18.52	12.69
63	38.9	2.4	2.8	7.0	17.96	11.90
65	34.6	2.9	4.3	5.8	16.64	8.32
66	29.9	1.4	2.8	3.0	10.05	5.40
67	36.5	1.6	4.1	5.9	16.15	11.88
70	33.6	1.9	3.5	4.4	13.17	7.55
70	47.8	3.2	2.4	6.8	14.33	7.71
72	29.1	1.1	3.8	3.7	12.58	8.70
73	30.5	1.5	3.9	3.9	12.84	7.74
75	23.7	2.3	5.3	4.0	16.68	6.85
80	43.5	2.2	3.5	5.7	13.18	8.11
84	55.0	1.5	3.1	6.6	11.95	9.27
89	31.9	1.9	3.0	4.3	13.37	7.35
92	28.6	2.0	2.8	4.7	16.40	9.51
			Mean Values			
70	35.7	2.0	3.6	5.0	14.35	8.57

See Table 1 for explanation of abbreviations.

TABLE 5.—SUBJECTS 50 YEARS OLD OR OVER WITH VASCULAR DISEASE AND DEPRESSED CONSCIOUSNESS (GROUP 5)

Age	*CBF*	$CMRO_2$	*CVR*	CDO_2	AO_2	CVO_2
50	29.6	2.7	3.3	5.6	18.80	9.76
50	47.4	1.6	2.0	5.3	11.04	7.75
54	53.0	2.6	2.1	8.1	15.34	10.53
56	14.5	1.1	7.7	2.4	16.49	9.22
57	40.1	2.7	4.4	6.5	16.08	9.29
58	23.9	1.3	3.9	4.6	19.08	13.53
65	35.3	2.8	3.9	5.0	14.17	6.34
66	26.9	1.8	4.9	3.9	14.55	7.71
66	44.9	2.5	4.1	9.1	20.37	14.73
	45.3	2.7	4.2	9.4	20.67	14.73
72	29.5	2.0	3.9	3.9	13.06	6.19
78	50.6	3.5	2.2	7.2	14.90	7.37
80	10.8	0.5	6.4	1.1	9.90	5.20
80	28.7	1.5	3.7	5.0	17.73	12.19
			Mean Values, Group 5			
64	33.5	2.1	4.1	5.2	15.51	9.22
			Mean Values, Groups 3, 4, 5 (Combined)			
66	35.2	2.1	3.8	5.2	14.91	8.86

See Table 1 for explanation of abbreviations.

TABLE 6.—EFFECTS OF BREATHING 10 PER CENT OXYGEN IN SUBJECTS 50 YEARS OLD OR OVER WITH CEREBRAL VASCULAR DISEASE

	CBF		AO_2		CVO_2		CDO_2		$CMRO_2$		*MBP*		*CVR*	
Age	*C*	*E*	*C*	*E*	*C*	*E*	*C*	*E*	*C*	*E*	*C*	*E*	*C*	*E*
63	41.7	48.8	17.39	14.90	11.12	8.55	7.2	7.2	2.6	3.1	112	105	2.7	2.2
67	25.7	28.0	17.03	14.20	13.03	9.98	4.4	4.0	1.0	1.2	150	148	5.8	5.3
69	27.5	33.3	17.94	12.97	11.76	7.32	4.9	4.3	1.7	1.9	122	129	4.4	3.9
72	29.5	32.0	13.06	9.17	6.19	3.04	3.9	2.9	2.0	2.0	114	108	3.9	3.4
75	36.5	45.9	16.85	12.56	9.64	7.38	6.2	5.8	2.6	2.4	100	104	2.7	2.3
78	37.0	56.4	15.12	10.52	9.36	7.19	5.6	5.9	2.1	1.9	86	93	2.3	1.7
80	10.8	16.4	9.90	8.31	5.20	4.35	1.1	1.4	0.5	0.6	69	75	6.4	4.6
81	34.7	51.2	12.49	8.76	3.79	3.11	4.3	4.5	3.0	2.9	151	168	4.4	3.3
					Mean Values									
73	30.4	39.0	15.00	11.42	8.76	6.37	4.7	4.5	1.9	2.0	113	116	4.1	3.3

See Table 1 for explanation of abbreviations.

the limited number of cases renders the change of no statistical significance. There was no significant overall change in mean arterial blood pressure, and dispersion similarly renders the reduction in mean cerebral vascular resistance of no statistical significance.

The reduction in mean arterial oxygen content attendant upon 10% oxygen inhalation is of about the same order as the increase in cerebral blood flow, and consequently mean cerebral oxygen delivery shows no significant change between control and experimental observations. The mean cerebral metabolic rate also shows no appreciable change during the relatively short period of hypoxia.

In 27 patients between the ages of 50 and 90 years, immediately after control determinations an atmosphere containing 5% carbon dioxide was inhaled over a 30-minute period, during the final 10 minutes of which cerebral hemodynamics and metabolism were again evaluated. The mean cerebral blood flow of the entire group shows a significant ($P < .001$) increase during this procedure. Because of a fairly consistent elevation in blood pressure, the change in mean cerebral vascular resistance observed in the entire group is of questionable significance. In view of a small increase in mean arterial oxygen content during carbon dioxide inhalation and the increase in mean cerebral blood flow, a significant ($P < .001$) increase in oxygen delivery resulted. No appreciable change is seen in the mean cerebral metabolic rate of the group as a whole as a result of CO_2 inhalation.

It should be pointed out that in a fairly large number of cases in this series there was no appreciable response of cerebral hemodynamics to carbon dioxide inhalation, while in others the increase in cerebral blood flow and decrease in cerebral vascular resistance were even more marked than is reflected by the change in the means of the series. It should also be pointed out that a significant ($P < .01$) increase in mean cerebral oxygen consumption can be noted in about half of the subjects, occurring with fairly good consistency among those in whom cerebral oxygen delivery was at a low level (below 4.9 cc./min./100 gm. brain) before carbon dioxide administration.

Discussion. CEREBRAL ARTERIOVENOUS OXYGEN DIFFERENCES. The results of this investigation make it again apparent that the cerebral arteriovenous oxygen difference cannot be relied on by itself to detect cerebral metabolic and hemodynamic changes when both occur simultaneously. Thus, although the mean cerebral arteriovenous oxygen differences in the various clinical groups were within 1 volume per 100 cc. of one another, significant differences from the normal in mean cerebral blood flow of those with cerebral vascular disease were demonstrated by the nitrous oxide procedure. These did not alter markedly the mean cerebral arteriovenous oxygen differences because of concurrent changes in mean cerebral oxygen consumption.

CEREBRAL BLOOD FLOW. It is noteworthy that the mean cerebral blood flow was markedly and practically equally reduced in the presence of the various clinical manifestations of cerebral vascular disease as exemplified by Groups 3, 4, and 5. The mean cerebral blood flow rates of these groups taken together were significantly lower than that of the group of elderly persons without clinical evidence of cerebral arteriosclerosis (Group 2). However, it must be assumed that such pathology was nevertheless present in the latter subjects in view of their increased mean cerebral vascular resistance and decreased mean cerebral

blood flow as compared to younger individuals without apparent cerebral vascular disease (Group 1).

The most rapid rate of blood flow seen in Group 1 was 72.6 cc. of blood/min./100 gm. of brain; in Group 2, 62.5 cc. of blood/min./100 gm. of brain; in Group 3, 60.7 cc. of blood/min./100 gm. of brain; in Group 4, 57.9 cc. of blood/min./100 gm. of brain; and in Group 5, 53.0 cc. of blood/min./100 gm. of brain. The slowest rates of blood flow seen in Groups 1 and 2 were 42.1 cc. of blood/min./100 gm. of brain in Group 1 and 24.7 cc. of blood/min./100 gm. of brain in Group 2. The upper extremes of cerebral blood flow in any group with cerebral vascular disease can therefore be said to exist within the range of the groups without clinical or experimental evidence of cerebral vascular disorder; and the lower extremes of cerebral blood flow in those persons without central nervous system pathology can be said to be within the range of those groups with cerebral vascular disturbances. Thus, individual determinations may be of questionable value in establishing cerebral hemodynamic abnormality.

The findings of a moderately to markedly reduced mean cerebral blood flow in the presence of obvious cerebral vascular disease was anticipated by Scheinberg[11] and Freyhan *et al.*[2]. It is hardly to be considered surprising that apparently asymptomatic elderly persons may show a similar though not so marked reduction in cerebral blood flow since it is well recognized that vascular disease may exist anywhere in the body without appreciable functional impairment. "The tendency to assume that normal human adults with no demonstrable signs of vascular disease are free from atheromatosis and thus differ qualitatively from patients with coronary occlusion or other definite evidence of atherosclerosis is generally incorrect and has led to a good deal of confusion. Since the population as a whole must be considered to have atheromatosis, according to the findings of the pathologists, there is no control group and comparisons of patients and normals are actually comparisons between different degrees of severity and different anatomic locations of atheromatous lesions"[3].

It is obvious from our results that such an intermediate stage between absence of vascular disease and vascular disease with functional impairment must exist in the central nervous system of many, if not most, clinically "normal" elderly persons. The overlapping distribution of cerebral blood flow values among the various clinical types of cerebral vascular disease and apparently normal individuals emphasizes the fact that within a wide range the rate of transportation of blood to the brain is by no means the only factor which may influence cerebral function. However, it must be recognized that relatively marked degrees of circulatory stagnation may by themselves influence the metabolic activity of the central nervous system.

Cerebral Vascular Resistance. The value for cerebral vascular resistance, representing the frictional opposition to the flow of blood through the cerebral vessels, would seem to be a valuable quantitative index of the extent of cerebral arteriosclerosis. However, since its calculation is based on mean arterial blood pressure and cerebral blood flow, it may be markedly influenced by changes in the latter due solely to variations in blood viscosity (anemia[4,13], polycythemia[4]), or functional increase (hypertension[5]) or decrease (acidosis[6,8]) of cerebral vascular tone. Thus, the value for cerebral vascular resistance in any individual must be interpreted with due consid-

eration of these factors. By comparing the *mean* values for cerebral vascular resistance in each of our groups, such factors as above noted are essentially equalized so that the differences in mean vascular resistance for practical purposes reflect changes associated with advancing age and/or clinical evidence of vascular disease in the brain. The finding of an elevated value in apparently normal elderly persons and in those with cerebral vascular disease confirms the impression that, if the influence of other factors could be cancelled out, cerebral vascular resistance would indicate quantitatively the degree of cerebral arteriosclerosis in both classes of subjects; but for reasons already noted, in individual persons the value need not depend upon the organic condition of the cerebral vessels, nor can it be reliably correlated with the clinical status. Thus, in an apparently normal elderly person the value of 4.4 was seen; and in comatose or mentally deteriorated elderly subjects values as low as 2.0 were noted. Such values would have little or no prognostic importance in individual cases.

Cerebral Oxygen Utilization. The mean oxygen consumption in clinically normal elderly patients, in spite of their completely adequate mental function, was significantly reduced from the mean value of individuals below the age of 50 years. There was little difference in mean cerebral oxygen utilization between clinically normal elderly patients, those with vascular disease as evidenced by mental changes, and those who were in coma. Although the mean value for young persons varies from 3.5 to 4 cc. of oxygen/min./ 100 gm. brain[7,14], in Group 2 seemingly normal cerebral function was observed in the presence of a mean cerebral metabolic rate of only 2.4 cc. of oxygen/min./100 gm. of brain. This is the more remarkable considering that cerebral metabolic rates as low as 1.3 were observed in the absence of recognizable mental deterioration. (In acute and subsequently prolonged reduction of cerebral oxygen consumption as seen in diabetic coma, Kety *et al.*[6] have noted that levels below 2.1 not only are associated with unconsciousness but almost invariably are followed shortly by death.)

Our observations indicate a lack of correlation between cerebral function and measurable cerebral oxygen utilization and blood flow, at least as influenced by age and vascular disease. A similar lack of correlation has been noted in hyperthyroidism[9,12,15] and hypothyroidism[9]. It is probable that cerebral function has a relatively minute energy requirement, fluctuations in which cannot be measured quantitatively by techniques now available; the oxygen consumption of cerebral tissue as determined by the nitrous oxide method probably represents almost in its entirety the trophic, or vegetative, metabolism which supports the structure and life of the cells.

Cerebral Oxygen Delivery. Any decrease in cerebral metabolic rate must be due either to a curtailed availability of nutriments to the cerebral cells or to failure of utilization of nutriments due to a depression of enzyme activity. In the absence of hypoglycemia, a diminution in oxygen availability or a primary disturbance of cerebral enzyme activity would therefore be the only explanation for the decrease in cerebral metabolic rate noted in most of our elderly subjects. Oxygen availability depends not only upon the actual quantity of oxygen delivered to the tissue but also upon the relative ease with which this oxygen can reach the enzyme systems. Although this ability cannot be quantitatively

measured in vivo by means now available, it is reasonable to believe that such diffusibility would vary in accordance with the velocity of blood flow, the concentration of oxygen in the arterial blood, the intracellular oxygen tension as regulated by the cerebral oxygen consumption, the facility of oxyhemoglobin dissociation, and a factor "X" representing the permeability of the "blood-brain barrier." Necessarily, because of limitations imposed by these factors, the rate of oxygen utilization at best can only approach that of oxygen delivery; under no circumstance is the blood oxygen so efficiently removed that the venous oxygen content is zero. Thus, given a sufficiently low oxygen delivery rate, there can be no question but that oxygen utilization will thereby be confined to the even lower level of oxygen availability. The considerable reduction in mean cerebral blood flow seen in the older age groups as compared to Group 1 would require an inversely proportional increase in mean arterial oxygen content in order to maintain the same mean rate of cerebral oxygen delivery as in the younger persons. This did not occur and as a result a marked decrease in mean cerebral oxygen delivery was noted in all the older age groups. The relationship between this finding and the reduced cerebral metabolic rate of the aged is not necessarily one of cause and effect. As already indicated, the extent to which oxygen delivery must fall before the reduction in oxygen availability impairs cerebral metabolism is at present not known, and probably varies in individuals.

Cerebral Hemodynamics and Oxygen Utilization During 10 Per Cent Oxygen or 5 Per Cent Carbon Dioxide Inhalation. It was in an effort to evaluate the importance of reduced oxygen availability that studies were performed on cerebral hemodynamics and metabolism of elderly persons as influenced by the inhalation of 10% oxygen or 5% carbon dioxide. It was noted that the resulting increase in mean cerebral blood flow and decrease in mean cerebral vascular resistance were not as marked in our subjects as in Kety and Schmidt's series[8], and in several of our experiments no significant changes were observed. These findings may indicate that many elderly persons have a diminished capacity for cerebral vasodilatation because of organic vascular disease or that the mechanism responsible for the vascular reaction is not as easily activated by hypoxia or hypercapnia as in the young. There is the additional possibility that in some elderly patients reduced oxygen delivery has already caused a relative vasodilatation; thus, further dilatation could not be so marked as that seen in younger persons.

It was found that, with few exceptions, an increase in cerebral blood flow attendant upon administration of 10% oxygen compensated for the hypoxemia to the extent of maintaining a cerebral oxygen delivery rate of at least 90% of the control value. Administration of 5% carbon dioxide, however, usually caused not only an increase in cerebral blood flow but also a minor increase in arterial oxygen content. The resulting increase in cerebral oxygen delivery was greater than 10% of the control value in all but 4 cases. In most instances in which cerebral oxygen delivery was less than 4.9 cc./min./100 gm. of brain before inhalation of carbon dioxide, there was observed an increase of 10% or more in the rate of cerebral oxygen consumption whether or not cerebral oxygen delivery increased to this extent. The nature of the change in the cerebral metabolic rate attendant upon carbon dioxide administration to subjects orig-

TABLE 7.—EFFECTS OF BREATHING 5 PER CENT CARBON DIOXIDE IN SUBJECTS 50 YEARS OLD OR OVER WITH CEREBRAL VASCULAR DISEASE

A. Cerebral Oxygen Delivery Below 4.9 cc./min./100 gm. of Brain (Control Value)

	CBF		*AO_2*		*CDO_2*		*$CMRO_2$*		*MBP*		*CVR*	
Age	*C*	*E*	*C*	*E*	*C*	*E*	*C*	*E*	*C*	*E*	*C*	*E*
56	14.5	37.2	16.49	17.72	2.4	6.6	1.1	2.4	112	160	7.7	4.3
66	29.9	58.4	10.05	12.15	3.0	7.1	1.4	2.2	83	93	2.8	1.6
70	34.8	28.4	12.15	13.02	4.2	3.7	1.0	1.9	145	144	4.2	5.1
70	18.8	38.5	10.66	11.50	2.0	4.4	0.6	2.3	151	162	8.0	4.2
70	20.4	45.2	10.35	11.33	2.1	5.1	1.0	2.5	135	172	6.6	3.8
70	33.6	53.8	13.17	13.98	4.4	7.5	1.9	2.1	116	150	3.5	2.8
70	31.1	51.0	13.21	14.38	4.1	7.2	1.7	2.1	110	128	3.5	2.5
70	37.5	52.8	12.31	13.49	4.7	7.1	2.0	1.9	114	140	3.1	2.7
72	42.7	53.6	11.29	11.37	4.8	6.1	1.8	2.0	108	128	2.5	2.4
73	25.5	32.7	17.11	19.25	4.4	6.3	2.2	2.2	96	134	3.8	4.1
75	63.6	94.5	4.20	5.38	2.7	5.1	1.5	2.6	89	105	1.4	1.1
77	27.8	29.3	15.31	15.88	4.3	4.7	1.4	1.6	112	139	4.0	4.7
80	30.6	81.4	13.88	14.58	4.3	11.9	2.0	2.8	82	110	2.7	1.4
80	24.0	20.2	11.93	12.42	2.9	2.5	0.6	0.6	110	111	2.4	3.2
89	31.9	81.6	13.37	14.46	4.3	11.8	1.9	2.0	96	106	3.0	1.3
					Mean Values							
73	31.1	50.6	12.37	13.39	3.6	6.5	1.5	2.1	111	132	3.9	3.0

B. Cerebral Oxygen Delivery 4.9 cc./min./100 gm. of Brain (Control Value) or Over

	CBF		*AO_2*		*CDO_2*		*$CMRO_2$*		*MBP*		*CVR*	
Age	*C*	*E*	*C*	*E*	*C*	*E*	*C*	*E*	*C*	*E*	*C*	*E*
50	29.6	40.2	18.80	19.67	5.6	7.9	2.7	1.8	98	105	3.3	2.5
57	43.4	66.8	11.61	12.39	5.0	8.3	2.5	2.5	135	150	3.1	2.3
60	33.5	89.9	14.98	15.78	5.0	14.2	2.5	2.6	90	95	2.7	1.0
63	36.4	41.8	18.52	19.76	6.7	8.3	2.1	2.6	105	113	2.9	2.7
65	34.6	46.1	16.64	17.60	5.8	8.1	2.9	2.7	148	185	4.3	4.0
66	31.9	46.0	18.71	20.04	6.0	9.3	2.8	3.3	123	139	3.9	3.0
72	41.1	35.4	12.03	12.66	4.9	4.5	1.9	1.6	130	123	3.2	3.5
78	50.6	77.0	14.29	14.99	7.2	11.5	3.5	3.9	110	126	2.2	1.6
78	32.0	37.1	15.25	15.88	4.9	5.9	2.3	2.6	86	98	2.7	2.6
78	34.2	36.9	14.78	15.62	5.1	5.8	2.1	2.0	89	106	2.6	2.9
84	55.0	59.6	11.95	13.19	6.6	7.9	1.5	2.5	168	193	3.1	3.2
91	44.1	51.4	14.29	15.15	6.3	7.8	2.3	2.2	90	100	2.0	2.0
					Mean Values							
70	38.9	52.4	15.15	16.06	5.8	8.3	2.4	2.5	114	128	3.0	2.6
					Mean Values, Parts A and B (Comb.)							
71	34.6	51.4	13.23	14.58	4.6	7.3	1.9	2.3	112	130	3.5	2.8

inally having a low rate of cerebral oxygen delivery is speculative; it might be the result of improved oxygen availability due to either better oxyhemoglobin dissociation, improved blood–brain barrier permeability, or increased cerebral oxygen delivery. However, an increase in oxygen delivery to presumably adequate levels frequently failed to influence the cerebral metabolic rate indicating that in such instances the impairment of oxygen utilization may not have been demonstrated by vascular accident, and in those with vascular disease associated with psychosis or impaired consciousness.

It was found that in the average elderly person, in spite of absence of clinical involvement of the nervous system, some degree of arteriosclerosis was evidenced by an increased cerebral vascular resistance and a reduction in cerebral blood flow from the values seen in the younger group. These changes were somewhat more

TABLE 8.—MEAN VALUES COMPARED

Class	*Age*	*CBF*		*AO₂*		*CVO₂*		*CDO₂*		*CMRO₂*		*MBP*		*CVR*	
Group 1	34	54.2		14.72		8.25		8.1		3.5		112		2.1	
Group 2	68*	42.5*		13.24		7.77		5.7*		2.4*		113		2.9*	
Group 3	63*	36.4*		15.04		8.97		5.5*		2.2*		138		3.8**	
Group 4	70*	35.7*		14.35		8.57		5.0*		2.0*		128		3.6**	
Group 5	64*	33.5*		15.51		9.22		5.2*		2.1*		112		4.1**	
Groups 3, 4, 5	66*	35.2**		14.91		8.86		5.2*		2.1*		112		3.8**	
Experimental		*C*	*E*	*C*	*E*	*C*	*E*	*C*	*E*	*C*	*E*	*C*	*E*	*C*	*E*
10% O_2	73	30.4	39.0	15.00	11.42	8.76	6.37	4.7	4.5	1.9	2.0	113	116	4.1	3.3
5% CO_2 CDO_2 <4.9	73	31.1	50.6†	12.37	13.39	7.39	8.89	3.6	6.5†	1.5	2.1†	111	132	3.9	3.0
5% CO_2 CDO_2 4.9 or >	70	38.9	52.4†	15.15	16.06	8.67	10.98	5.8	8.3†	2.4	2.5	114	128	3.0	2.6
5% CO_2 All cases	71	34.6	51.4†	13.23	14.58	7.96	9.82	4.6	7.3†	1.9	2.3	112	130	3.5	2.8

* Significantly different from Group 1 values.
** Significantly different from Group 2 values.
† Significantly different from control values.
See Table 1 for explanation of abbreviations.

pendent upon a low oxygen availability, but rather upon reduced enzymatic activity. This is even more probably the case in the many instances of reduced cerebral oxygen consumption with cerebral oxygen delivery of 4.9 cc./min./100 gm. of brain or more.

Summary and Conclusions. Cerebral hemodynamics and oxygen consumption were investigated in subjects 50 years of age or older without evidence of cerebral vascular or parenchymatous central nervous system disease, in those with cerebral arteriosclerosis as marked in elderly persons with clinical evidence of cerebral vascular disease, whatever the manifestation. The mean levels of cerebral oxygen consumption of elderly persons with or without evidence of central nervous system vascular disease was significantly reduced from that of younger subjects but appeared to have little relationship to the clinical manifestations, if any, of vascular involvement.

The attempt at altering cerebral oxygen delivery by means of 10% oxygen inhalation was not demonstrably successful, and no overall change in

cerebral oxygen consumption was seen. Relatively minor changes in cerebral blood flow and cerebral vascular resistance were rendered statistically insignificant by dispersion of values within the small series. The inhalation of 5% carbon dioxide caused an increase in cerebral blood flow similar to, but not so extensive as, that reported for younger subjects[8]. A reduction in cerebral vascular resistance appeared to be of questionable significance in persons with marked cerebral vascular disease. In most instances in which cerebral oxygen delivery had been less than 4.9 cc./min./100 gm. of brain, carbon dioxide administration was accompanied by an increased rate of cerebral oxygen consumption. The data suggest that decreased cerebral enzyme activity and/or impaired oxygen availability may contribute to the changes in central nervous system function so frequently encountered in the aged.

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PRELIMINARY REPORT OF THE ANTIRHEUMATIC ACTION OF HEPARIN AND PARITOL–C IN GOUT AND RHEUMATOID ARTHRITIS*

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THE observation that the anticoagulants heparin and Paritol-C† have a favorable antirheumatic action has prompted this report on the effect of these drugs in the rheumatic disorders. The antirheumatic effect of heparin and Paritol was first noted during the treatment of patients with acute myocardial infarctions who had concomitant arthritis. There was observed during the period of the anticoagulant therapy with heparin or Paritol a decrease of the swelling and the pain and an increased mobility in the involved joints.

A review of the literature revealed that this antirheumatic action had been previously reported for both heparin and Dicumarol. In 1946 Wassen and Zander[15] reported improvement in cases of "acute polyarthritis" and "erythema nodosum" but not in "chronic arthritis" while on Dicumarol therapy. Glazebrook and Cookson[7] hypothesized that heparin and Dicumarol might be beneficial in rheumatoid disorders. Improvement was obtained in 8 cases of rheumatoid arthritis treated with heparin by Glazebrook and Wrigley[8]. Donzelot and Kaufman[3,4,5,6] reported a favorable antiarthritic action with heparin, but not with Dicumarol.

Materials and Methods. Thirteen patients with various types of rheumatic disorders were studied. There were 5 cases of acute, non-tophaceous gouty arthritis, 6 cases of active subacute rheumatoid arthritis, and 2 cases of acute nonspecific arthritis.

The patients were all treated with either Heparin Repository** or Paritol. No other medication was used during the course of treatment with these drugs. Heparin was given subcutaneously in dosages of 200 to 300 mg. every 12 hours. Paritol was administered intravenously, 3 to 4 mg./kg. of body weight, in 5 or 10% solution every 12 to 24 hours. Treatment was continued for varying lengths of time depending on the response. The anticoagulant effects of these drugs were measured by the Lee-White coagulation time[11], the Quick one-stage prothrombin time[12], and the plasma antithrombin level[10]. The erythrocyte sedimentation rate was determined before, during, and after therapy in all cases. Serum uric acid levels were obtained in all cases of gout.

Results. The 5 cases of gout (Table 1) responded favorably to either hepa-

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† A polysulfuric acid ester of polyanhydromannuronic acid supplied by Wyeth, Inc.

** Heparin Repository was supplied through the courtesy of Dr. Stanton M. Hardy, Lederle Laboratories, Division American Cyanamid Co.

rin or Paritol. Case 3 had been taking therapeutic doses of colchicin and salicylates with no benefit. When these were discontinued, Paritol was administered with a good response. Case 2 had an exacerbation 1 month after the first course of treatment, but when Paritol was given again, a similar favorable response occurred. There was no significant change in the serum uric acid or sedimentation rate during or after therapy.

Table 2 shows the results obtained with heparin or Paritol in cases of rheumatoid arthritis and acute arthritis of an undetermined nature. Each

TABLE 1.—CASES OF GOUT TREATED WITH HEPARIN AND PARITOL

Case	*Age*	*Sex*	*Serum Uric Acid (mg./100 cc.)*	*Drug*	*Dosage*	*Duration* ℞	*Joints Involved*	*Results*	*Duration of Attack Before* ℞ *(Days)*	*Onset of Clinical Gout (Year)*
1	52	M	7.6	Heparin	100–200 mg. q 12 hr.	8 days	1	Complete remission in 36 hr.	6	1944
2	64	M	9.6	Paritol	3.0–4.0 mg./kg. q 12 hr.	2½ days	1	Complete remission in 24 hr.	2	1933
3	37	M	13.5	Paritol	3.5–4.0 mg./kg. q 12 hr.	4 days	1	Complete remission in 96 hr.	2	1949
4	67	M	7.4	Paritol	4.0 mg./kg. q 12 hr.	36 hr.	1	Complete remission in 48 hr.	2	First attack
5	56	M	6.0	Paritol	4.0 mg./kg. q 12 hr.	48 hr.	1	Complete remission in 48 hr.	3	1945

TABLE 2.—SUMMARY OF CASES OF ARTHRITIS TREATED WITH HEPARIN AND PARITOL

Type	*Case*	*Stage*	*Class*	*Age*	*Sex*	*Drug*	*Dosage*	*Duration* ℞	*Results*
Subacute Rheumatoid Arthritis	1	III	II	51	F	Heparin	200 mg. q 12 hr.	3.5 days	Decrease in pain. No change in swelling. Grade IV.
						Paritol	3.5–4.0 mg./kg. q 12–24 hr.	13 days	Decrease in pain and swelling. Grade III.
	2	II	II	25	F	Heparin	200 mg. q 12 hr.	2 days	Decrease in pain and swelling in 48 hr. Grade III.
						Paritol	3.5–4.0 mg./kg. q 12–24 hr.	31 days	Complete remission of pain and swelling throughout course of therapy. Grade II.
	3	II	III	58	M	Paritol	3.0–4.0 mg./kg. q 12 hr.	6 days	Decrease in pain and swelling in 96 hr. Grade III.
	4	III	II	50	M	Heparin	200–300 mg. 12 hr.	4.5 days	Decrease in pain and swelling in 48 hr. Grade III.
	5	III	II	19	F	Paritol	4.0 mg./kg. q 12 hr.	7 days	No effect. Grade IV.
with Spondylitis	6	II	II	55	M	Paritol	4.0 mg./kg. q 12–24 hr.	29 days	Decrease in pain. No change in swelling. Grade IV.
Undiagnosed Polyarthritis	1			26	M	Paritol	3.0–4.0 mg./kg. q 12 hr.	5 days	Complete remission of pain and swelling in 5 days.
Undiagnosed Monoarthritis with Pericarditis	1			45	M	Paritol	4 mg./kg. q 12 hr.	2 days	Complete remission of symptoms and signs in 48 hr.

of the patients with rheumatoid arthritis has been classified according to the stage of the disease, degree of functional impairment, and estimation of therapeutic response of rheumatoid activity as recommended by the American Rheumatism Association Committee on Therapeutic Criteria[14].

Five of the 6 patients with rheumatoid arthritis reported subjective improvement with either heparin or Paritol. Four patients showed objective improvement in 40 to 96 hours, manifested by a decrease in swelling of actively involved joints. One of these patients (Case 1) failed to show a decrease in swelling while on heparin, but did respond to Paritol. In Case 5, that of a patient with rheumatoid spondylitis and peripheral joint disease, improvement was only subjective. The spondylitis was moderately advanced but inactive, and the classification as indicated in Table 2 refers to the peripheral joint disease in this patient. The patient with arthritis and pericarditis obtained remission of signs and symptoms after 2 days of Paritol therapy. The electrocardiogram returned to normal 3 days after cessation of treatment.

In Cases 1 and 2, heparin therapy was instituted, but this was discontinued because of severe local reactions. In Case 4 the heparin was stopped after a satisfactory response was noted. This patient, however, had a recurrence of signs and symptoms 2 weeks later. When heparin was reinstituted, satisfactory control of arthritic symptoms was again obtained as long as the drug was continued.

Paritol seemed to be the more satisfactory drug. Its effect, however, was only temporary after therapy was discontinued and the effect disappeared within approximately 2 weeks. In addition, mild untoward side-effects such as have been previously reported were noted in 2 of the 11 cases treated with Paritol[10,13]. No significant change was observed in the sedimentation rate with either drug.

Discussion. To our knowledge, this is the first report of the beneficial effect of heparin and Paritol in acute gouty arthritis. The 5 cases responded dramatically to either heparin or Paritol, with approximately 80% reduction in pain, swelling, and tenderness within 24 hours. Within 48 to 96 hours a complete remission occurred in each case. In no case was so-called "rebound phenomenon" observed as has been reported after therapy with ACTH[2].

The anticoagulant drugs, heparin and Paritol, have a definite antirheumatic effect. The mechanism of their action is unknown. Several theories have been postulated: (a) an anticoagulant action[15]; (b) an antihyaluronidase action[8,9]; (c) an antiexudative action[4]; (d) an antianaphylactic action[7]; and (e) an influence on an antigen–antibody reaction[7]. It would at least seem that the favorable antirheumatic responses obtained were not primarily due to the anticoagulant action of the drugs used, because such responses occurred in instances where the commonly accepted anticoagulant control effects were not maintained.

The minimum effective dose of these drugs has not been determined in this small series of cases. Early in the study the amount of either drug necessary to produce an adequate anticoagulant effect was used, but as the study progressed this amount was found to be unnecessary and the drugs were administered at increased intervals. Further, it was noted that patients receiving Dicumarol for thromboembolic disease had relapses of rheumatic disorders while under adequate anticoagulant control*. No beneficial results

* Adequate Dicumarol effect is considered to be achieved with a prothrombin time between 22 and 38 seconds in undiluted plasma and a control of 13 to 15 seconds.

were noted in 6 additional cases of subacute rheumatoid arthritis treated with Dicumarol for a period of 2 to 4 weeks. An increased heparin tolerance was found in the 3 cases of rheumatoid arthritis in which the determinations were made. Abrahams and Glynn[1] have reported an increased heparin tolerance in cases of active rheumatic fever. The full significance of this finding has not been determined.

The long-term management of rheumatoid arthritis with heparin or Paritol is impractical at present. We do not propose that either of these drugs is an effective therapeutic agent in cases of rheumatoid arthritis. However, the rapid and complete remission obtained in the 5 cases of acute gout strongly suggests definite antirheumatic activity in these drugs. Related substances may be developed which will exhibit greater antirheumatic action.

Summary. 1. The anticoagulants, heparin and Paritol, were used in the treatment of 13 cases of rheumatic diseases.

2. Complete remission of all clinical signs and symptoms occurred in the 5 cases of gout.

3. These drugs appear to have practical value in acute gouty arthritis which is unresponsive to classical therapy.

4. Favorable antirheumatic effects were observed in cases of active rheumatoid arthritis during therapy.

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THE USE OF MERCURIAL DIURETICS IN THE TREATMENT OF BROMIDE INTOXICATION*

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Treatment of the clinical entity caused by bromide intoxication has been for the most part unsatisfactory. The administration of sodium chloride appears to be the only accepted therapeutic regimen. This procedure is based upon the observation that increased intake of chlorides increases the excretion of bromides from the body. It has been shown that this increased elimination of the bromide ion results from a change in the concentration ratio between chlorides and bromides in the body fluids and that this ratio depends upon the ratio of intake of the respective ions. This factor appears to be maintained through a simple mechanism, namely, that bromides displace chlorides during periods of bromide administration and chlorides displace bromides when ingestion of the former is increased. The displaced bromides are then excreted by the kidneys. In this concept it is assumed that the kidneys make no distinction between the two halogens, but, rather, function to maintain the total halogen content of the extracellular fluids at the normal level.

Unfortunately, the sodium chloride treatment of bromide intoxication cannot be considered highly satisfactory. The bromides are eliminated slowly, making the period of recovery from the symptoms prolonged. Excretion rates vary in different individuals, of course, dependent upon the amount of salt intake and the condition of renal function. The graph in Goodman–Gilman's book shows the effect of sodium chloride administration on the rate of elimination of bromides and demonstrates the necessity of a period of approximately 23 days for the serum bromide level to drop from 350 to 130 per 100 cc.[5]. Various clinical reports are in line with this observation. Cross writes that it takes from 3 to 6 weeks to clear up the symptoms of this entity using sodium chloride therapy[4]. Wohl and Robertson found an average of 23 days[10] and Perkins' figure was an average of 17 days[8] for complete disappearance of symptoms.

A review of the literature reveals a sparsity of reports of investigation with the object of improving therapeutic results in this entity. This has been due, at least in part, to the conclusion of some clinicians that too rapid mobilization of bromides from the tissues may temporarily increase the serum

* Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

bromide level and thus aggravate clinical symptoms. Such a therapeutic paradox could conceivably have drastic consequences. However, this fear has been controversial among authors, and there is no proof to justify this belief.

The use of salt, either alone or in combination with other drugs, has been used extensively in the treatment of these patients. Wohl and Robertson treated 7 patients with the combination of desoxycorticosterone acetate (DOCA) and sodium chloride[10]. The average time for clearance of symptoms was 9.75 days, and the blood bromide level was reduced by 50% in 4 to 8 days, as compared to 8.5 to 14.5 days for patients treated with sodium chloride alone. One patient was treated with DOCA only without beneficial effect. Bondurant and Campbell reported good results with adrenal cortical extract therapy in 7 cases of bromide intoxication[1].

Harris and Derian administered 750 mg. of niacinamide daily to 6 patients; 4 had no sodium chloride, but 2 were given 6 grams per day[6]. The average time required for the symptoms to disappear was approximately 5 days. The symptoms cleared even though a high blood bromide level was maintained. The addition of sodium chloride caused a gradual decrease in the blood bromide level. Apparently no adequate pharmacological explanation of this phenomenon has been offered.

Recently, Cornbleet has shown that ammonium chloride produces more rapid elimination of bromide than does sodium chloride administration[3].

Unfortunately, clinical investigators have not utilized the results of the investigation of Palmer and Clarke[7] and Bodansky and Modell[1]. Their experiments on dogs have thrown a new light on the method of elimination of bromides from the body. They have shown that there exists a differential excretion of bromides and chloride ions by the kidneys. This investigation has promoted better understanding of the mechanism of bromide retention in the body. On the basis of their work these investigators suggested a new approach to therapy.

Prior to the investigation of Bodansky and Modell it was the accepted theory that the kidney does not differentiate between the chloride and bromide ions in its reabsorption and rejection of electrolytes. The experimental basis for this work had been performed on rabbits.

In the investigation of preferential excretion of chloride a formula has been devised to express the relation between the chloride and total halogen ratio in the blood and urine. In the case of rabbits, K has a value of 1 in the following formula:

$$K = \frac{\text{Bromide (Urine)}}{\text{Bromide (Serum)}} = \frac{\text{Total Halide (Urine)}}{\text{Total Halide (Serum)}}$$

In contrast to the rabbit experiments, investigations using the dog indicate that, in this animal, the kidney excretes chloride preferentially[1]. Here the value for K was found to be approximately 0.4, with an average but constant chloride intake. The value for K was temporarily increased when either bromide or chloride was injected into the dog. Values up to 0.7 were reached, but were never as high as those reported for the rabbit.

These observations led to the following conclusions: First, that the storage of bromide depends on the differential excretion of chloride and bromide, together with the ratio of these two ions in the ingested food; second, that chloride administration in the treatment of bromism increases excretion of bromides by increasing the total halide excretion as well as the fraction of the bromide in it.

The preferential excretion of chloride is the result of the fact that the bromide ion moves slightly more rapidly than the chloride ion; therefore, it is more rapidly reabsorbed from the glomerular filtrate in the tubules than the chloride ion[7].

Bodansky and Modell found that after salyrgan injections there was an enormous increase in the excretion of total halide consisting of both increased chlorides and bromides, and, in addition, a rise in the bromide–halide ratio of the urine, resulting in the increase of the value of K in the excretion formula previously referred to.

The precise mechanism by which mercurial diuretics act upon the kidney is still unknown. Various investigators have shown that there is no increase in glomerular filtration, but that the diuresis is due to the decreased rate of tubular reabsorption[9].

If the preferential excretion of chloride ultimately depends upon the extent of preferential reabsorption of bromide in the tubules, one would expect that mercurial diuretics should reverse this situation. On this premise, we decided to investigate the value of mercurial diuretics in the treatment of bromism.

It is interesting to note that other diuretics (such as urea, sodium, sulfate, and large amounts of water) all failed to increase the excretion of halides. Theophylline, however, did increase total halide and bromide excretion[1].

TABLE 1.—EFFECT OF MERCUHYDRIN ON BROMIDE EXCRETION WHEN SODIUM CHLORIDE WAS GIVEN AT BEGINNING OF TREATMENT (CASE 1)

		Urine				
Day	*Serum Br level, mg./100 cc.*	*24-hr. vol., cc.*	*Br level, mg./100 cc.*	*Total Br excreted gm.*	*NaCl given*	*Mercuhydrin given*
1	284	940	294 (?)	2.76	+	
2	266	Specimen discarded by mistake			+	
3		3,800	120	4.56	+	+
4		5,270	95	5.06	+	
5	212	4,475	70	3.13	+	
6	198	2,750	147	4.04	+	+
7	186	2,340	109	2.55	+	
8	175	3,000	75	2.25	+	
9	147	2,700	109	2.93	+	+
10		2,125	92	1.91	+	
11		2,450	78	1.91	+	
12	100	2,980	86	2.56	+	+

Procedure. During the treatment of 2 cases of chronic bromide poisoning with 6 gm. of sodium chloride added to the daily diet, 2 cc. of mercurial diuretic were injected intramuscularly at intervals of 3 or more days. The urinary excretion of bromide was observed in each case. The levels in

the blood and 24-hour urine were determined daily by the gold chloride method. In a 3rd case ammonium chloride was substituted for the sodium chloride.

Findings. CASE 1 (D.W.) This 36-year-old man was admitted to the hospital in a confused, stuporous state with a bromide blood level of 284 mg. per 100 cc.

His treatment regimen was started with 6 gm. of sodium chloride daily added to his diet. Mercuhydrin* in 2 cc. doses was given intramuscularly on the 3rd, 6th, 9th, and 12th hospital days. The laboratory findings in Table 1 show the effect of mercuhydrin on bromide excretion. These are further illustrated by the graphic chart in Fig. 1. The patient became mentally clear on the 5th hospital day and rapidly regained his normal status.

COMMENT. The mercuhydrin increased bromide excretion in this patient by increasing urinary bromide concentration without increasing urine volume.

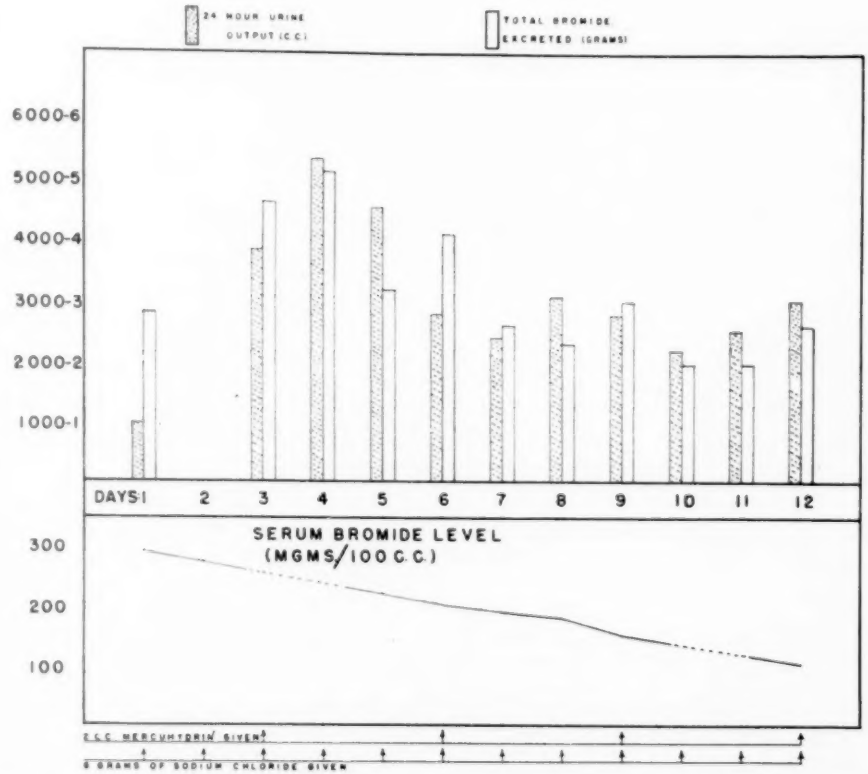

FIG. 1.—The influence of administration of sodium chloride alone and in combination with mercuhydrin on the total urinary bromide excretion and serum bromide levels, Case 1.

CASE 2 (C.W.). This 42-year-old man was admitted to the hospital in a confused state. He exhibited symptoms of catatonia. The blood bromide level was found to be 250 mg. per 100 cc.

Salt was withheld from his diet until the 8th hospital day. The mercuhydrin was given on the 4th, 7th, and 10th days. Be-

* Trade name for mercurial diuretic manufactured by Lakeside Laboratories, Inc.

ginning with the 8th hospital day daily doses of 6 gm. of sodium chloride were added to this regimen. The laboratory findings in Table 2 show the effect of mercuhydrin on bromide excretion. These are illustrated by the graphic chart in Fig. 2. The patient was almost mentally clear on the 6th hospital day despite the blood bromide level of 175 mg. per 100 cc. His mental condition rapidly improved and he was able to leave the hospital in approximately 2 weeks.

She was given ammonium chloride, 1 gm. 4 times daily, and mercuhydrin injections on the 3rd and 6th days of the investigational period. The laboratory findings are recorded in Table 3 and the effect of mercuhydrin on the excretion of bromide is illustrated by the graphic chart in Fig. 3.

COMMENT. The mercurial diuretic increased the bromide excretion in this case in a manner similar to that in the

TABLE 2.—EFFECT OF MERCUHYDRIN ON BROMIDE EXCRETION WHEN SODIUM CHLORIDE WAS WITHHELD AT BEGINNING OF TREATMENT (CASE 2)

		Urine				
Day	*Serum Br level, mg./100 cc.*	*24-hr. vol., cc.*	*Br level, mg./100 cc.*	*Total Br excreted, gm.*	*NaCl given*	*Mercuhydrin given*
1	205					
2	186	835	142 (?)	1.18		
3	186	460	38	0.17		
4		2,650	83	2.20		+
5		2,100	23	0.48		
6	175	3,150	26	0.82		
7	163	3,140	75	2.35		+
8	149	2,780	40	1.11		
9	127	3,300	95	3.13	+	
10	106	2,850	100	2.85	+	+
11		4,000	67	2.68	+	
12		3,950	43	1.70	+	

COMMENT. The mercuhydrin alone increased urinary bromide excretion both by increasing urinary concentration and increasing the volume of urine excreted. These were further increased by the addition of sodium chloride.

CASE 3 (M.G.). This 42-year-old woman was admitted to the hospital in an agitated state with visual and auditory hallucinations. The blood bromide level was 396 mg. per 100 cc. She was treated by the neuropsychiatric service until the 15th hospital day, before being transferred to the medical service. At this time her mental condition had improved and the blood bromide level was found to be 100 mg. per 100 cc.

previous 2 cases. We could suppose that the bromide excretion was increased in 2 ways, that is, by increased urine volume, and by increased urine volume and increased urinary bromide concentration.

Discussion. The findings in these cases strongly suggest that mercuhydrin increases the excretion of bromide, both by increasing urinary volume and also by increasing the bromide concentration in the urine. Unfortunately, we have no determination of plasma and urinary chlorides taken simultane-

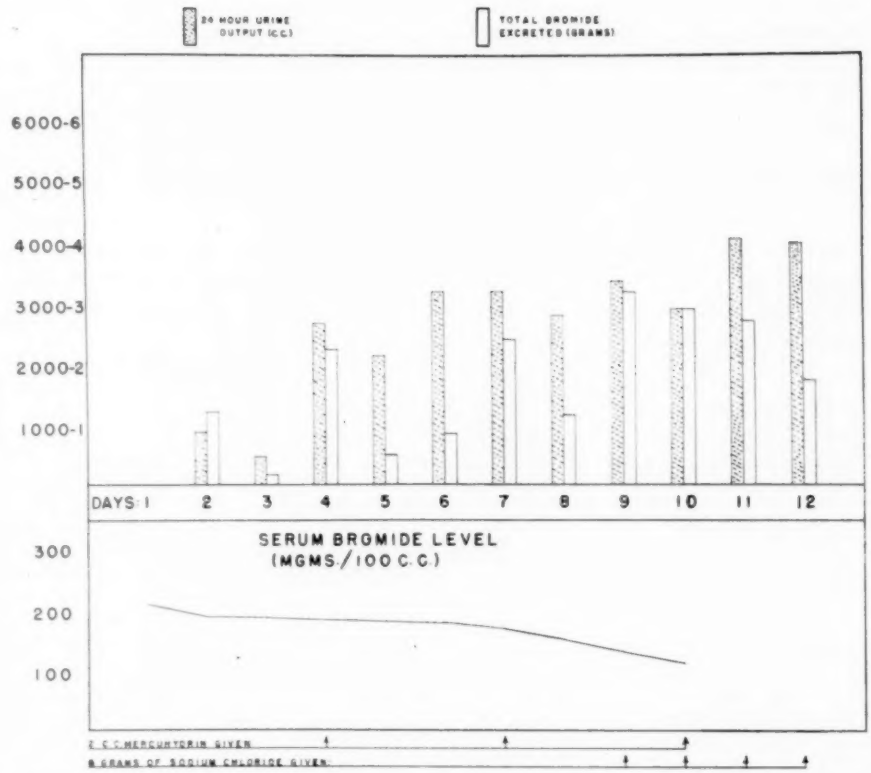

FIG. 2.—The influence of administration of mercuhydrin alone and in combination with sodium chloride on the total urinary bromide excretion and serum bromide levels, Case 2.

TABLE 3.—EFFECT OF MERCUHYDRIN ON BROMIDE EXCRETION WHEN AMMONIUM CHLORIDE WAS GIVEN AT BEGINNING OF TREATMENT (CASE 3)

		Urine				
Day	*Serum Br level, mg./100 cc.*	*24-hr. vol., cc.*	*Br level, mg./100 cc.*	*Total Br excreted gm.*	*Ammonium chloride given*	*Mercuhydrin given*
1		925	56	0.51	+	
2	95	800	70	0.56	+	
3	61	2,000	117	2.30	+	+
4	33 (?)	680	78	0.53	+	
5	67	475	60	0.28	+	
6	67	2,630	86	2.26	+	+
7	60	415	38	0.15	+	

ously with the bromides which would indicate to what extent mercuhydrin influenced the preferential excretion of chlorides, or, in other words, the value of the K ratio in the formula presented.

Administration of sodium chloride and mercuhydrin each increase the urinary bromide concentration, as combination with the administration of either sodium chloride or ammonium chloride.

The rapid elimination of bromide from the body fluids is still the most rational management of bromide intoxication. The serum bromide level consistently decreased under the influence

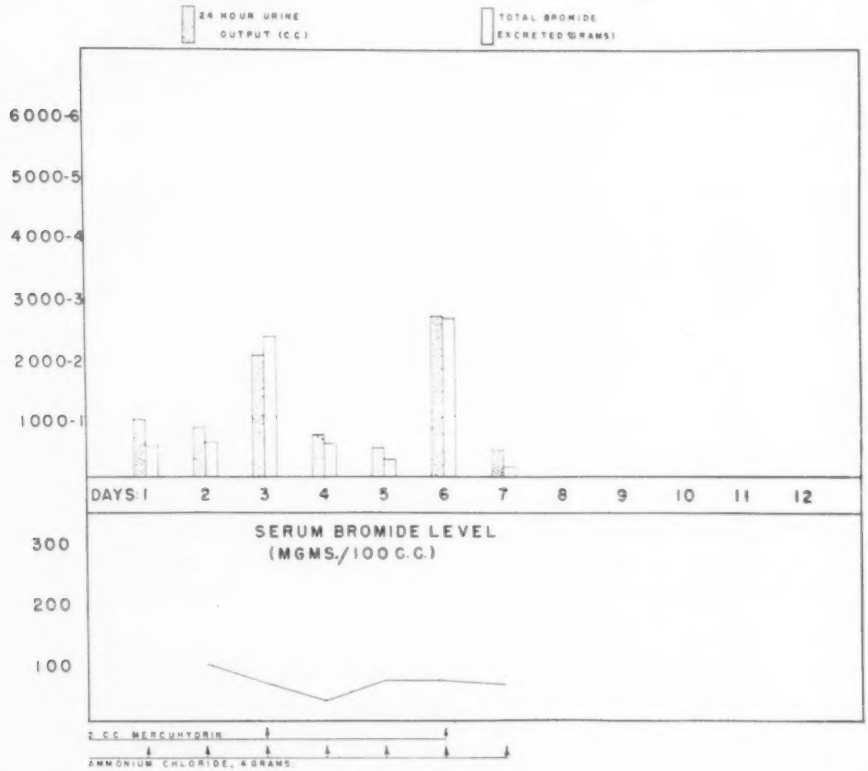

FIG. 3.—The influence of administration of ammonium chloride alone and in combination with mercuhydrin on the total urinary bromide excretion and serum bromide levels, Case 3.

shown in Cases 1 and 2. When ammonium chloride was given instead of sodium chloride, excretion of bromide was increased in a manner similar to that seen in Cases 1 and 2.

From this study one may conclude that mercuhydrin is an effective addition to the therapy for bromide intoxication. This drug should be used in of the drug. For those who fear a "quick mobilization of bromide" by radical therapy mercuhydrin will prevent an increase in blood bromide level that may result from large amounts of chloride administration. There were no findings indicating an exacerbation of symptoms from quick mobilization of bromides after treatment with the

mercurial drug. It is reasonable to assume that the rapid elimination of this ion by the kidney under the influence of a mercurial diuretic rapidly clears the blood stream of the toxic drug.

Summary. 1. The effect of mercuhydrin on bromide excretion has been investigated in 3 cases of bromide intoxication.

2. The administration of this mercurial diuretic increased bromide excretion by increasing urinary bromide concentration and the volume of urine excreted. Administration of sodium chloride acted similarly and the effect of these 2 agents was additive when used together.

3. When ammonium chloride was substituted for sodium chloride, bromide excretion was similarly enhanced as a result of an increase in the urinary volume and in the urinary concentration of the noxious ion.

4. It is suggested that the most effective therapy of bromide intoxication is the combined administration of ammonium chloride or sodium chloride and mercurial diuretics.

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CLINICAL OBSERVATIONS ON A NEW EPINEPHRIN-LIKE COMPOUND, METHOXAMINE

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Methoxamine is a new synthetic sympathomimetic compound which differs from epinephrin primarily in having methoxy instead of hydroxy groups on the benzene ring. The complete chemical name is beta-(2,5-dimethoxyphenyl) - beta - hydroxyisopropylamine hydrochloride. It has been reported that the drug produces a potent and sustained pressor response in experimental animals[3]. The chief therapeutic application has been in the prevention of the drop in blood pressure associated with spinal anesthesia[5]. Methoxamine differs from epinephrin, norepinephrin, and most other pressor amines in that it does not induce ventricular fibrillation or other arrhythmias even in the cyclopropane sensitized heart of the experimental animal[13]. Since the absence of such effects may be of considerable advantage in the clinical use of a pressor drug, the present study was undertaken to determine the action of methoxamine on the rhythmic function of the human heart.

Methods. In previous studies[7-10] the action of drugs on cardiac rhythmicity (pacemaking function) was studied by 3 methods, by which were determined a) the effect on the cardiac standstill induced by pressure on the carotid sinus, b) the effect on the ventricular rate of complete heart block, and c) the effect on sinus rhythm. The cardiac standstill which can be induced in many elderly males by pressure on the carotid sinus is due to a temporary inactivity of the sinus node and to a failure of formation of secondary rhythmic centers. If a drug increases cardiac rhythmicity, the standstill is prevented by the formation of a new pacemaker or by the restoration of the activity of the normal pacemaker, the sinus node. If a drug has no effect on cardiac rhythmicity, the standstill will be consistently reproduced. In previous reports[7,8], it was shown that epinephrin and many related compounds effectively prevented the standstill. In a recent study[10], it was pointed out that the ventricular rate of heart block also serves as an excellent means of testing the effect of drugs on ventricular rhythmicity. The ventricular rate is relatively stable and is uninfluenced by extraneous factors. The evidence that a drug increases ventricular rhythmicity is an increase in the ventricular rate following the administration of the drug. The effect of a sympathomimetic pressor drug on the sinus rate is more complex and is the result of two actions: a) stimulation of the sinus node, tending to increase heart rate, by a direct sympathomimetic effect on the myocardium, and b) suppression of the sinus node, tending to a bradycardia mediated by a reflex vagus action, resulting from the rise of pressure in the aorta and the carotid sinus. A bradycardia following the administration of a pressor compound indicates that the drug has little or no direct action on cardiac rhythmicity.

* Fellow of the National Heart Institute in the Department of Cardiology directed by Dr. George C. Griffith.

This study was aided by the Dorothy H. and Lewis Rosenstiel Foundation.

Procedures and Results. ACTION ON CAROTID SINUS INDUCED CARDIAC STANDSTILL. The effect of methoxamine was studied in 6 patients in whom it was possible to induce a cardiac standstill of 5 seconds or longer by compression of the right carotid sinus. An electrocardiogram was first made showing the induced standstill. Three blood pressure readings were recorded. Methoxamine in doses varying from 5 mg. to 10 mg. was injected intravenously. Electrocardiograms were then taken at frequent intervals, with observation of the effect of pressure on the carotid sinus. Blood pressure readings were also recorded. In each instance during the period of pressor action following the administration of the drug, the cardiac standstill was easily and consistently reproduced (Fig. 1). The rise in blood pressure occurred within a minute after the completion of the injection. The maximum increase ranged from 40 mm. systolic and 10 mm. diastolic to 100 mm. systolic and 30 mm. diastolic pressure. This cardiac response to methoxamine is in sharp contrast to that of epinephrin. This drug consistently abolished the carotid sinus induced cardiac standstill even in small non-pressor doses, through the formation of rhythmic foci[8].

ACTION IN COMPLETE HEART BLOCK. Methoxamine was administered to 6 patients with complete heart block. The dose was 5 mg. given by a rapid intravenous injection. Blood pressures were recorded and an electrocardiogram made before the administration of the drug. Following the injection, a continuous record was made for 5 minutes and thereafter at 1-minute intervals. Three blood pressure readings were made during the first minute and then at intervals of 1 minute. In 5 patients, there was no change in the ventricular rate and in one instance there was a reduction in rate of 10 beats per minute. The maximum increase in blood pressure ranged from 55 mm. systolic and 10 mm. diastolic to 80 mm. systolic and 40 mm. diastolic pressure. A typical response to methoxamine is shown in Fig. 2. The ventricular rate is unchanged although a pronounced

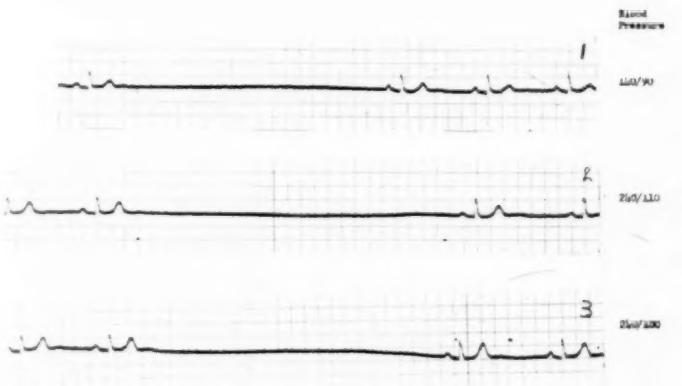


FIG. 1.—Strip 1: a cardiac standstill of 4.6 seconds induced by pressure on the right carotid sinus, blood pressure, 140/90. Strip 2 (taken 2 min. after an intravenous injection of methoxamine, 8 mg.): and induced standstill of 5.6 seconds; blood pressure, 240/110. Strip 3 (taken 4 min. after the drug): Standstill induced; blood pressure, 240/100.

pressor response is induced. This ventricular response is also in sharp contrast to that produced by epinephrin in heart block. This drug consistently induces a definite and sustained rise in ventricular rate[10].

ACTION ON SINUS RHYTHM. *Methoxamine.* The action of methoxamine was studied in 20 patients with sinus rhythm. After a control electrocardiogram was made and the blood pressure recorded, the drug was injected intravenously. The dosage was as follows: 10 mg. in 2 patients, 5 mg. in 7, 4 mg. in 7, and 3 mg. in 4 patients. A continuous electrocardiogram was made for 5 minutes and thereafter at intervals of 1 minute for 15 minutes. Blood pressures were recorded at intervals of 1 minute. A bradycardia consistently occurred coincidental with the rise in blood pressure. The maximum reduction in the pulse rate ranged from 16 to 61 beats per minute. The maximum pressor response ranged from a rise of 10 mm. systolic and no rise in diastolic to an increase of 110 mm. systolic and 40 mm. diastolic pressure. The maximum pressor reactions and heart rate responses are shown in Table 1.

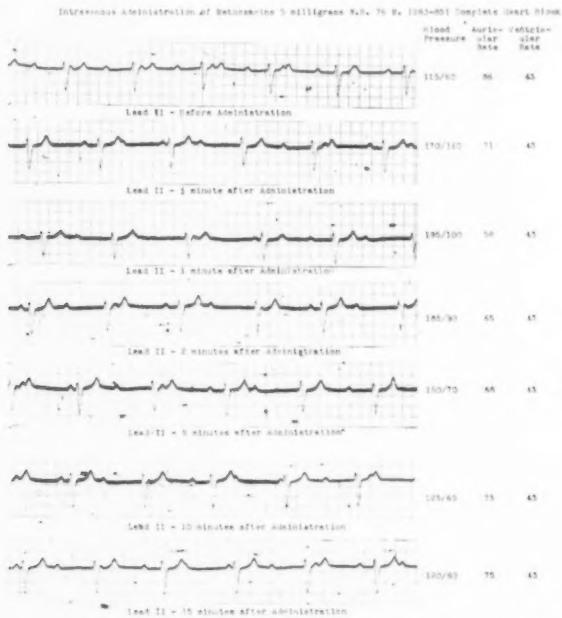


FIG. 2.—Upper strip: complete heart block; blood pressure 115/60; ventricular rate, 43 per minute. Lower strips (taken ½ min., 1, 2, 5, 10, and 15 min. after an intravenous injection of 5 mg. of methoxamine): blood pressure rose to 195/100 and dropped to 120/60, but the ventricular rate remained unchanged.

It is to be noted that there is a marked variation in the intensity of the responses and that the degree of bradycardia is not closely related to the intensity of the pressor effect. Typical reactions to methoxamine are shown in Figs. 3, 4 and 5. In addition to the bradycardia, other vagal effects such as sinus arrhythmia, prolongation of the P-R interval, nodal and ventricular escape were observed (Figs. 5 and 8). In 3 patients, a comparison was made

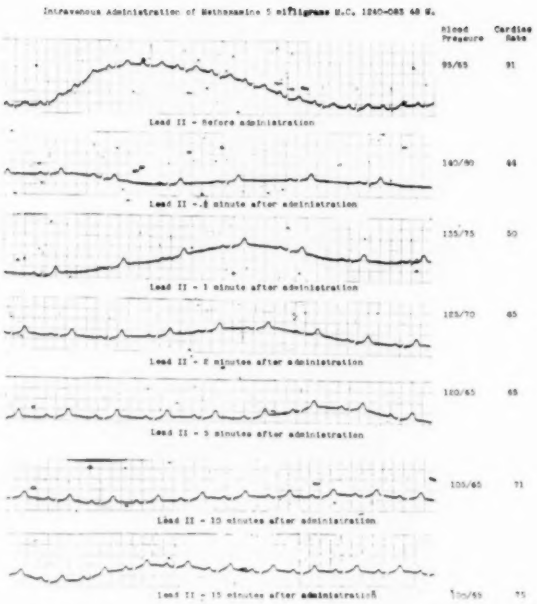


FIG. 3.—Upper strip: sinus tachycardia; rate, 91 beats per min.; blood pressure 95/65. Lower strips (taken ½ min., 1, 2, 5, 10, and 15 min. after an intravenous injection of 5 mg. of methoxamine): maximum slowing of heart rate to 44 beats per min. shown in 2nd strip; maximum blood pressure, 140/80.

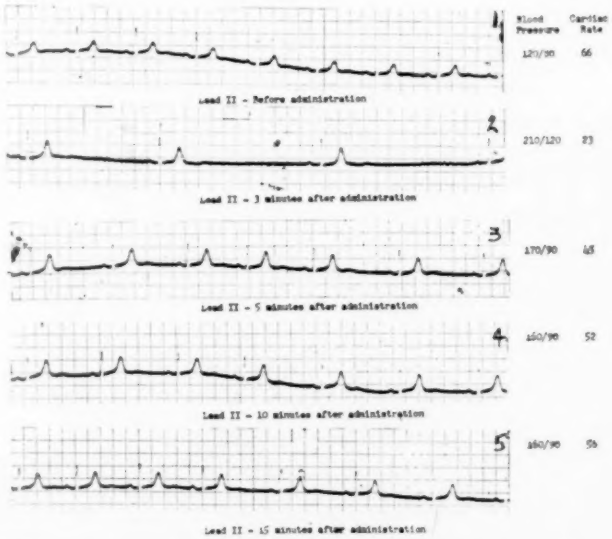


FIG. 4.—Strip 1: a sinus rhythm; rate, 66; blood pressure, 120/80. Strip 2 (taken 3 min. after an intravenous injection of 8 mg. of methoxamine): rate, 23 per minute; blood pressure, 210/120. Strips 3, 4, and 5 (taken 5, 10 and 15 min. after the injection of the drug): gradual reduction in blood pressure and rise in heart rate; sinus arrhythmia present. In this patient carotid sinus pressure had no effect on the heart rate.

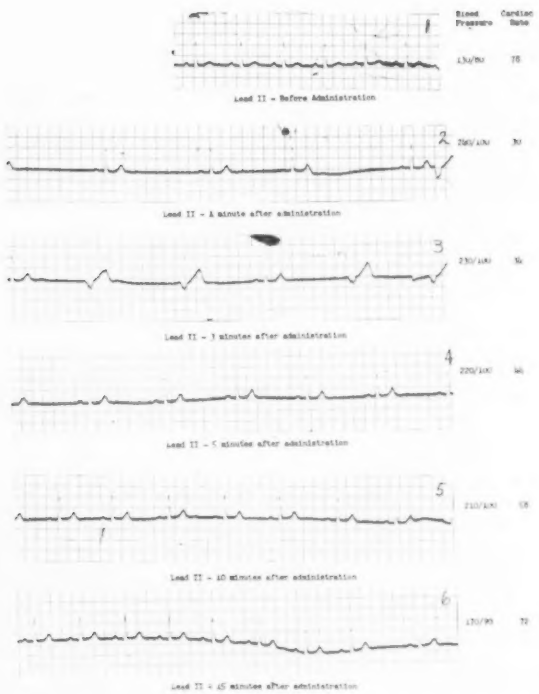
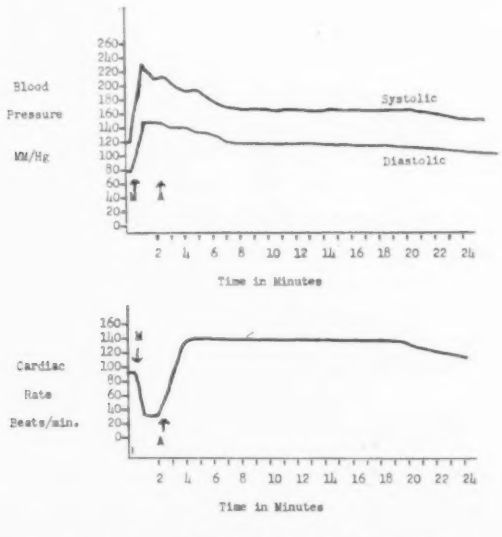


FIG. 5.—Upper strip; rate 78, blood pressure 130/80. Strips 2, 3, 4, 5 and 6, taken 1, 3, 5, 10, and 15 min. after an intravenous injection of 10 mg. of methoxamine; marked bradycardia to 30 beats per min. and ventricular escape (last complex in strip 2, and most of the complexes in strip 3). Blood pressure rose to 240/100.



Effect of Atropine on the Action of Methoxamine

FIG. 6.—Upper graph: the prompt increase in blood pressure after the intravenous administration of 5 mg. of methoxamine (M). Lower graph: the pronounced reduction in heart rate after methoxamine and the effect of an intravenous injection of atropine at A.

of the response to external carotid sinus pressure with that of the administration of methoxamine. In each instance, carotid comparison was ineffective while methoxamine induced a marked bradycardia (Fig. 4).

TABLE 1.—MAXIMUM Pressor and Heart Rate Responses after the Administration of Methoxamine

Patient	*Rise in B.P. (mm. Hg.) syst./diast.*	*Decrease in Heart Rate (beats per min.)*
P.H.	80/30	47
M.C.	45/25	47
V.P.	60/25	19
M.T.	70/35	32
D.D.	40/30	35
A.M.	45/20	29
I.D.	40/30	28
H.M.	50/20	38
N.W.	10/0	39
P.D.	30/20	22
I.W.	110/70	61
B.P.	45/20	19
W.C.	110/20	48
G.Q.	100/20	15
D.C.	90/40	35
P.D.	30/20	22
B.P.	45/20	19
B.C.	75/40	60
E.W.	30/15	38
H.G.	15/15	27

Atropine. The effect of atropine was studied in 11 patients with sinus rhythm. In 5 patients atropine was administered during the methoxamine induced bradycardia and in 6 patients, atropine was given prior to the administration of methoxamine. The first procedure was as follows: methoxamine was injected intravenously in doses of 4 mg. in 4 patients and 5 mg. in 1 patient. This was followed by the characteristic pressor response and bradycardia. The average reduction in heart rate was 39 beats per minute. Three minutes after the administration of methoxamine and during the period of bradycardia, atropine sulfate, 0.8 mg., was injected intravenously. The bradycardia was promptly replaced by a rise in heart rate, which averaged 23 beats per minute above the pre-experimental level (Fig. 6). In the second procedure, methoxamine was injected intravenously in doses of 3 mg. in 2 and 4 mg. in 4 patients. The pressor and heart rate reactions were recorded. The maximum reduction in rate ranged from 19 to 60 beats per minute with an average of 39 beats per minute. After the blood pressure and pulse had returned to the pre-injection level, atropine sulfate, 0.8 mg., was injected intravenously. Three minutes later, methoxamine was again injected intravenously. There was a slight slowing of the heart lasting about 1 minute which was followed by a pronounced and sustained increase in rate. The maximum increase ranged from 3 to 47 beats per minute and averaged 22 beats per minute above the pre-experiment level.

Subjective Sensations. The rapid administration of methoxamine in doses resulting in a pronounced pressor effect was associated with a few and mild subjective sensations. A dull headache occurred in a few instances with the more intense pressor responses. An infrequent complaint was a sense of fullness in the chest and neck which was not severe in any case. A prickly feeling in the forehead and a sensation of "goose pimples" was frequently noted. A desire to void was also a common sensation. However, the acute apprehension, severe chest oppression, palpitation, and throbbing in the neck, which attend the administration of epinephrin in pressor doses, were not associated with the intravenous injection of methoxamine.

Administration of Methoxamine in Paroxysmal Supraventricular Tachycardia. Keys and Violante[4] have shown that neosynephrin induces a brady-

cardia mediated through the vagus nerve. Youmans and his associates[15] utilized this vagal action in the therapy of paroxysmal supraventricular tachycardia. They showed that a paroxysm was frequently terminated by a rapid intravenous injection of neosynephrine. The following are brief histories of 2 patients in whom methoxamine was administered for this purpose.

and blood pressure were not obtainable. At this time, 10 mg. of methoxamine were injected rapidly by vein. Within 1 minute, the blood pressure rose to 110 mm. systolic and 70 mm. diastolic. The electrocardiogram showed a sinus rhythm which persisted with a normal blood pressure (Fig. 7). The change in the circulatory status of the patient was very dramatic.

Patient J. S., a male, 66 years of age, gave a history of attacks of palpitation for 15 years. The duration of the attacks was from 1 to 12 hours and they occurred about every

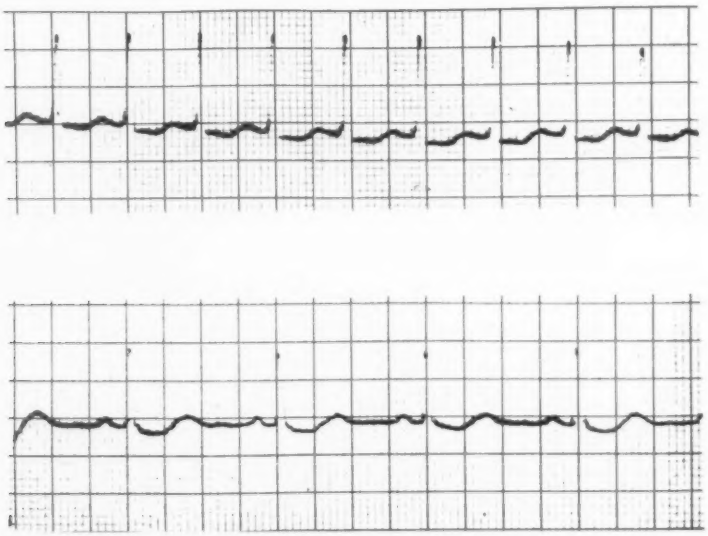


FIG. 7.—Electrocardiogram of patient T. G. Upper strip: a supraventricular tachycardia, rate 150 per min. Lower strip (taken 1 min. after a rapid intravenous injection of 10 mg. of methoxamine): sinus rhythm, rate 74 per min.

Patient T. G.,* a 64-year old woman, had experienced 4 attacks of tachycardia over a period of 2 years. The duration of the attacks was from 2 to 10 hours. They had been terminated by the oral administration of quinidine and a sedative. Four days after a cholecystectomy she developed a tachycardia of abrupt onset. An electrocardiogram showed a supraventricular tachycardia. The patient received quinidine by mouth and one dose of 0.2 gm. intramuscularly. Cedilanid, 1.6 mg., was administered intravenously without effect. Twenty hours after the onset of the attack, the patient was in shock and the pulse

3 or 4 months. He was studied in several paroxysms and the electrocardiogram showed that the mechanism was supraventricular tachycardia. He was seen in an attack which had been present for about an hour. The electrocardiogram showed a supraventricular tachycardia, rate 160 (Fig. 8, strip 1). The blood pressure was 124 mm. systolic and 86 mm. diastolic. Methoxamine, 8 mg., was injected rapidly by vein. Within 1 minute the ectopic rhythm reverted to a sinus rhythm, interrupted by one ventricular extrasystole (Fig. 9, strip 2). The blood pressure rose to 220 mm. systolic and 100 mm. diastolic. Sinus

* Clinical data supplied by Dr. Milton H. Uhley.

rhythm persisted which for a short time was associated with a prolongation of the P-R interval (Fig. 8, strips 3 and 4).

Discussion. Since the introduction of epinephrin as a therapeutic agent some 50 years ago, a large number of synthetic substitutes have been studied experimentally and clinically. However, only a few were found to possess advantages over the original drug and are in clinical use. Epinephrin and most of the related pressor compounds increase cardiac contractility resulting in an increase in cardiac output. They also increase cardiac rhythmicity leading to a rise in heart rate and the development of arrhythmias. In certain hypotensive states decreased peripheral vascular tone may be an important factor, and vasoconstrictor drugs may be of value[2]. The hypotension associated with a myocardial infarction reduces greatly the blood flow in the coronary vessels and pressor drugs have been recommended in order to counteract this effect[1]. The ischemic myocardium is predisposed to arrhythmias including ventricular fibrillation[14] and the administration of a pressor drug which increases cardiac rhythmicity is hazardous. Stutzman *et al.*[13] in the experimental animal demonstrated that methoxamine does not induce ventricular fibrillation during cyclopropane anesthesia. Under similar experimental conditions, epinephrin and nor-epinephrin

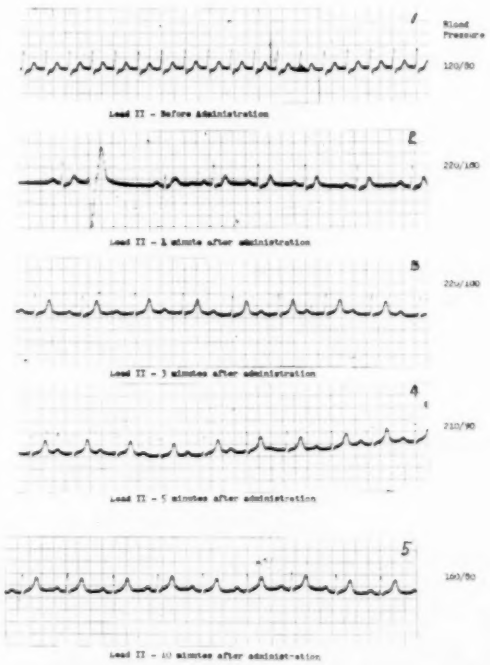


FIG. 8.—Electrocardiogram of patient J.S. Strip 1: a supraventricular tachycardia, rate 160 per min. Strip 2 (taken 1 minute after a rapid intravenous injection of 8 mg. of methoxamine): sinus rhythm; rate, 76 per min.; 1 ventricular extrasystole appeared. Strips 3, 4, and 5 (taken 3, 5, and 10 min. after the administration of the drug): strips 3 and 4 show a prolongation of the P-R interval.

consistently induce this fatal arrhythmia. Our present clinical studies indicate that methoxamine does not increase the rhythmic property of the human heart. Thus it would appear that methoxamine possesses favorable features as a pressor drug. In addition to the absence of an unfavorable cardiac action, the reflex inhibition of the heart may have some advantage as a tachycardia is frequently present in hypotensive states.

The slowing of the heart following the intravenous administration of methoxamine is abrupt and usually very pronounced. The abolition of the bradycardia by atropine indicates that this reaction is mediated through the vagus nerve. Stimulation of the vagus innervation of the heart is a means of terminating the paroxysms of supraventricular tachycardia. Reflex activation of the vagus by compression of the carotid sinus may be effective but frequently fails. The failure is probably due to the fact that a hyperactive cardio-inhibitory response to carotid sinus compression is seen frequently only in individuals above 50 years of age and in males. In younger individuals and especially in females, carotid sinus pressure usually elicits little or no reaction[9]. The vagal inhibition of the heart by methoxamine was not influenced by age or sex and was not related to the response elicited by external compression of the carotid sinus. The more consistent and pronounced cardiac inhibition induced by methoxamine may be due to the fact that a rise of pressure within the arteries activates all four afferent pathways concerned with cardiac slowing, that is, those arising from both carotid sinuses and the aortic arch. The pressor effect may also be of value as in some instances a severe hypotension may be present during a paroxysm of tachycardia. This is illustrated in the first patient.

Stutzman *et al.*[13] pointed out that in earlier studies[12] phenylephrin (neosynephrin) was the only one of 26 sympathomimetic compounds studied which was equally as innocuous as methoxamine in the experimental animal during cyclopropane anaesthesia. Keys and Violante[4] demonstrated a pronounced bradycardia in man following the administration of phenylephrin which resembled the response to methoxamine observed in the present study. A study of the comparative effects of these compounds is desirable and is planned. The following observations appear to have some bearing on their relative activities. One of us has demonstrated that phenylephrin in proper dosage can abolish a carotid sinus induced cardiac standstill[8]. This is in contrast to the ineffectiveness of methoxamine. We have noted ectopic ventricular activity with periods of ventricular ectopic beats, after the administration of phenylephrin for the shock following coronary occlusion. In one instance of myocardial infarction, a supraventricular tachycardia treated by intravenous phenylephrin was followed by a ventricular tachycardia. Recently Lu and Melville[6] showed that while moderate doses of phenylephrin did not increase cardiac contraction, large doses did lead to myocardial stimulation. Methoxamine in the largest doses employed produced no change in heart action, rate, or amplitude. These observers stated that methoxamine was the only sympathomimetic agent tested which did not induce myocardial stimulation. These observations, although not conclusive, suggest that methoxamine possesses a lesser tendency to cardiac stimulation than does phenylephrin.

Conclusions. Methoxamine in doses producing a pronounced pressor re-

action does not increase the rhythmic function of the human heart.

This is shown by the following: a) The drug does not prevent the carotid sinus induced cardiac standstill; b) it does not increase the ventricular rate in heart block; and c) there is a definite slowing of the heart rate following the intravenous administration of the drug.

The bradycardia is abolished or prevented by atropine, indicating that it is mediated through the vagus nerve.

The pronounced vagal effect induced by the drug can be utilized in the therapy of supraventricular tachycardia.

It is suggested that the absence of a cardiac stimulating action in a pressor drug may be of advantage in the therapy of certain hypotensive states.

We are indebted to Dr. Donald S. Searle of Burroughs, Wellcome and Co. for the supply of methoxamine. This compound has the commercial name, Vasoxyl.

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ANTIBIOTIC SYNERGISM AND ANTAGONISM IN A SUBACUTE EXPERIMENTAL STREPTOCOCCUS INFECTION IN MICE*

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A number of reports from this laboratory have dealt with the effect of combinations of antibiotics on experimental infections in mice. These infections, caused by *Streptococcus pyogenes* or *Klebsiella pneumoniae,* were acute and fulminating, produced by intraperitoneal inoculation of the bacteria, and resulted in death usually within 36 hours. They were treated with 1 dose of the antibiotics under study 1 hour after infection or by 3 doses administered within 12 hours after infection. By this technique interference with the therapeutic action of penicillin by chloramphenicol[8], aureomycin[9], terramycin[9], and sulfadiazine[3], and interference with the action of streptomycin by aureomycin, chloramphenicol, and terramycin[7] have been demonstrated. It would be valuable to know whether a more chronic infection might respond similarly to protracted administration of drug combinations.

This report concerns a subacute infection in mice caused by *Streptococcus pyogenes* which has proved useful as a means of studying treatment with combinations of antibiotics over a more extended period to demonstrate antagonistic and synergistic effects.

Materials and Methods. White Swice mice weighing 20 to 25 gm. were used. The *Streptococcus pyogenes* strain C203 has been employed in previous work in this laboratory[8]. It was grown in 5% sheep blood broth at 37°C. for 18 hr., and passed weekly through mice to maintain its virulence.

Commercial crystalline potassium penicillin G, streptomycin sulfate, and bacitracin (Lot B-480420†) were dissolved in sterile 0.85% sodium chloride solution to make stock solutions of 20,000 units/cc., 50,000 mcg./cc., and 5,000 units/cc., respectively. Synthetic crystalline chloramphenicol (Lot 134006**), aureomycin hydrochloride (Lot 7-6116‡), and terramycin hydrochloride (Lot WBW 507019††) were dissolved in salt solution and sterilized by Seitz filtration to make stock solutions of 1.0 or 2.0 mg./cc. These stock solutions were stored at 4°C. for 2 to 3 weeks except for aureomycin which was quick-frozen and stored at −20°C. Suitable dilutions of stock solutions were prepared in sterile saline solution for the daily treatment doses.

Mice were infected by injecting 0.1 cc. of a 10^{-4} dilution of an 18-hr. culture of *S. pyogenes* into the left thigh muscle[2]. This inoculum contained 3000 to 5000 organisms and produced death in 90 to 100% of the animals. Treatment with antibiotics was started 24 hr. after infection and continued

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† Supplied by Dr. L. S. Smith, Commercial Solvents Corp.

** Supplied by Dr. G. Rieveschl, Parke, Davis & Co.

‡ Supplied by Dr. S. Hardy, Lederle Laboratories.

†† Supplied by Dr. H. H. Anderson, University of California.

at 24 hr. intervals for 5 days. The antibiotics were administered intraperitoneally in 0.2 cc. of saline solution. When 2 antibiotics were used, they were injected separately, one directly after the other. The mice were observed for 14 days after the last treatment and deaths were recorded. Groups of not less than 20 mice were used for each antibiotic or combination of antibiotics. The statistical significance of results was calculated by the chi square method.

In an initial experiment several untreated mice were sacrificed daily and their organs cultured to observe the course of the infection. This was done by smearing uniform cross sections of the organs on blood agar plates[5] and estimating the number of characteristic colonies after incubation at 37°C. for 24 hours. Organs cultured included: a) left thigh muscle, b) left inguinal lymph node, c) liver, d) spleen, e) heart blood, f) lung, and g) bone marrow from the right femur. The number of colonies on the blood agar plate permitted a semi-quantitative estimate of the distribution of bacteria in the animal.

TABLE 1.—DISTRIBUTION OF STREPTOCOCCI IN MICE SACRIFICED AT INTERVALS AFTER INTRAMUSCULAR INFECTION

Day after infection	*Condition of mouse*	*Proportionate number of bacteria cultured from organs*						
		Muscle	*Node*	*Liver*	*Spleen*	*Heart*	*Lung*	*Bone marrow*
1	Lesion slightly indurated	Con	0	0	0	0	0	0
		24	0	0	0	0	0	0
2	Lesion slightly indurated	Con	0	0	1	0	0	0
	" " "	Con	0	0	0	0	0	0
	" " "	Con	0	0	0	0	0	0
3	Lesion slightly indurated	Con	0	0	0	0	0	0
	Lesion moderately indurated	Con	0	0	0	0	0	0
	" " "	Con	0	0	0	0	0	0
4	Lesion markedly indurated	Con	Con	0	0	0	0	0
	" " "	Con	Con	60–80	0	8	2	0
	Moribund	Con	4	Con	Con	Con	Con	50–60
5	Lesion markedly indurated	Con	Con	Con	60–80	80–100	31	1
	Lesion moderately indurated	Con	0	0	0	0	0	0
	Moribund	Con	1	80–100	12	80–100	7	6
6	Lesion moderately indurated	Con	17	0	0	3	0	0
	Moribund	Con	Con	19	8	Con	9	0
	"	Con	Con	Con	Con	Con	Con	7
	"	Con	Con	Con	Con	Con	Con	38

Key: Con = Confluent growth
0 = No growth
1–100 = Number of colonies on standard plating (see text).

Results. This infection is characterized by a uniformly high mortality. Of 110 infected but untreated control mice in the several experiments described in this report, 105 (95.4%) died. Of these 105 mice, 98 (93.3% died between the 5th and the 8th day after infection, with an average survival time of 6.6 days. These mice were all injected with 0.1 cc. of a 10^{-4} dilution of the original culture. However, the number of organisms injected did not materially affect the survival time, as illustrated by smaller series where the averages were respectively 6.2 days for mice receiving 0.1 cc. of a 10^{-2} dilution, 6.7 for a 10^{-3} dilution, 6.4 for a 10^{-4} dilution, and 6.6 days for a 10^{-5} dilution.

The infected mice showed local swelling in the thigh within 1 or 2 days after infection. This swelling increased, accompanied by limitation of motion, reddening, and frequently gangrene of the foot below the site of infection. For several days there were no symptoms of systemic illness, but for about 24 hr. prior to death, the animals showed signs of generalized, progressive infection with toxic depression. Cultures of mice sacrificed

daily (Table 1) indicated that during the early days of the infection the bacteria remained localized in the indurated muscle which became infiltrated and abscessed. On the 4th day, coinciding with the development of systemic illness in some of the mice, bacteria could be cultured occasionally from the heart blood and from various other organs. Bacteremia and generalized infection increased in the 5th and 6th days, during which most of the animals became moribund and died. All mice that were cultured during this period showed widespread dissemination of bacteria.

This infection was amenable to antibiotic therapy. Penicillin, in a total amount of 180 mcg. given in 5 daily doses, cured all mice. They showed only slight and temporary swelling of the site of the injection during the early days of treatment (Fig. 1). A smaller total dose of 90 mcg. cured a substantial number, 60%, and significantly delayed the deaths that occurred in the group (Fig. 2). A still smaller total dose of 9 mcg. cured between 15 and 50% in several experiments (Fig. 3, Table 2).

This subacute infection was used to determine the action of combinations of antibiotics. Both synergistic and antagonistic effects were encountered with daily injections of drugs for 5 days. Fig. 3 and Table 2 (Exp. 1) illustrated marked synergism between 9 mcg. of penicillin, which in this experiment cured only 15%, and 500 mcg. of streptomycin, which cured only 10%; the combination cured 75%. In another experiment (Table 2, Exp. 2) with 9 mcg. of penicillin and 480 mcg. of bacitracin, given in the usual 5 daily doses, 40% survived in each group treated with 1 drug alone,

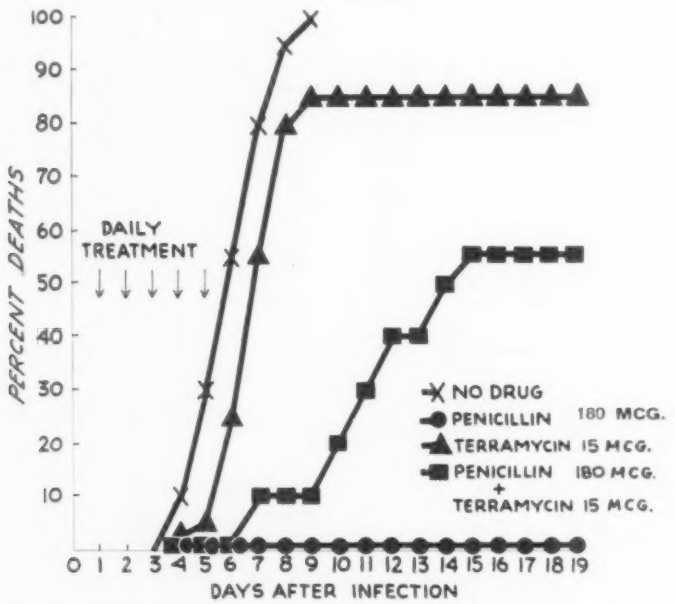

FIG. 1.—Chronic streptococcus C203 infection in mice treated with penicillin and terramycin.

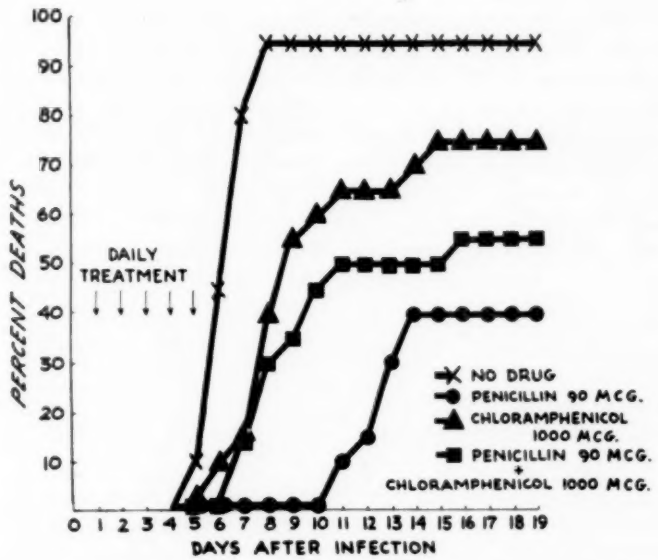

FIG. 2.—Chronic streptococcus C203 infection in mice treatment with penicillin and chloramphenicol.

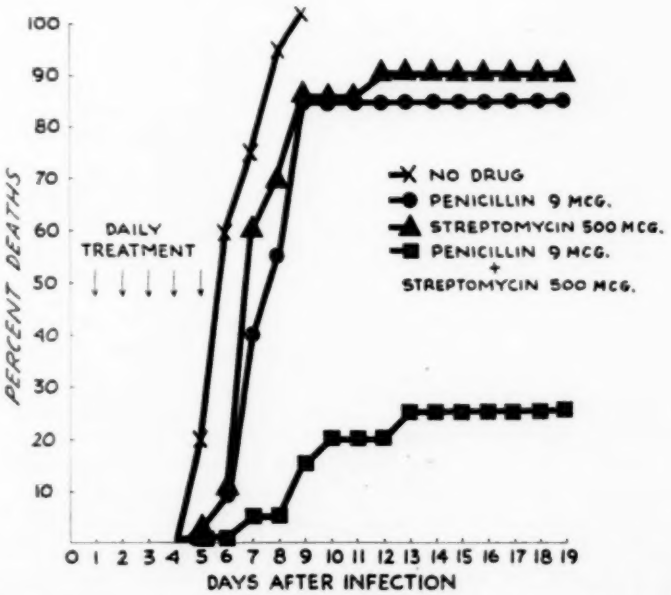

FIG. 3.—Chronic streptococcus C203 infection in mice treated with penicillin and streptomycin.

whereas 80% survived in the group receiving both antibiotics. In a third experiment (Table 2, Exp. 3) relatively inactive amounts of penicillin, aureomycin, and terramycin failed to result in synergism.

Marked antagonism was observed when 15 mcg. of terramycin interfered with 180 mcg. of penicillin which alone cured 100% of the mice; the combination cured only 45% (Fig. 1, Table 2). Moderate interference with the same dose of penicillin was demonstrated by 1000 mcg. of chloramphenicol (Table 2). Fig. 2 shows the effect of this dose of chloramphenicol in another experiment where 90 mcg. of penicillin was administered. Here the ultimate cure rates of 60% with penicillin alone and 45% with the combination, are not significantly different, but the chloramphenicol abolished the prolonged survival resulting from the action of penicillin alone. On the 10th day after infection (5th day after termination of treatment) the difference between single and multiple antibiotics was great. All animals treated with penicillin only were alive, whereas 45% of those receiving penicillin and chloramphenicol had succumbed. The relatively ineffective dose of 15 mcg. of aureomycin (30% survival) was neither synergistic with, nor antagonistic to, penicillin.

TABLE 2.—THE EFFECT OF COMBINATIONS OF ANTIBIOTICS ON THE SURVIVAL RATE IN A SUBACUTE STREPTOCOCCAL INFECTION OF MICE

Exp. No.	*Antibiotics and Total Dose per Mouse (dosage in mcg.)*	*% Survivors*	*Significance of Results*	
			Interpretation	*P*
1	None (Controls)	0		
	Penicillin 9	15		
	Streptomycin 500	10		
	Penicillin 9, Streptomycin 500	75	Synergism	0.001
2	None (Controls)	10		
	Penicillin 9	40		
	Bacitracin 480	40		
	Penicillin 9 + Bacitracin 480	80	Synergism	0.03
3	None (Controls)	0		
	Chloramphenicol 1000	50		
	Aureomycin 15	30		
	Terramycin 15	15		
	Penicillin 180	100		
	Penicillin 180 + Chloramphenicol 1000	70	Antagonism	0.03
	Penicillin 180 + Aureomycin 15	80	Not signif.	0.11
	Penicillin 180 + Terramycin 15	45	Antagonism	0.001
	Penicillin 9	50		
	Penicillin 9 + Aureomycin 15	75	Not signif.	0.25
	Penicillin 9 + Terramycin 15	35	Not signif.	0.3

The total dose of antibiotic was administered to groups of 20 mice over a period of 5 days by daily intraperitoneal injections, beginning 24 hr. after infection.

Discussion. This technique, adapted from Eagle[2], offers a means of establishing a slower, less drastic infection in mice than the overwhelming intraperitoneal infection used previously. The infective process proceeds in an orderly manner from the site of injection via the lymphatics to the regional lymph nodes. As transient bacteria reach the blood stream they are at first filtered out by spleen and liver, until (rather suddenly) these filters break down and overwhelming septicemia

results in death. This infection lends itself to treatment by divided doses of antibiotic over a period of days, rather than by 1 or 3 doses administered shortly after infection. Such long-term treatment of an infection which has been allowed to become established in the animal resembles more closely situations met in clinical practice. It seems reasonable to conclude that results obtained with the treatment of this type of experimental disease may be more applicable to spontaneous human infections. That certain aspects of antibiotic antagonism have been demonstrated again by this method seems to broaden the possible significance of the phenomenon. The previously observed synergism between penicillin and streptomycin[4,6] is again shown, suggesting that this method may be useful to investigate the existence of other such relationships among the increasing number of antibiotics. Thus synergism between bacitracin and penicillin acting on a hemolytic streptococcus is demonstrated, similar to the effect of this combination on spirochetes[1] and enterocci[1,6].

Further possibilities of the method are offered by the periodic culturing of the animals during the infection, treatment, and post-treatment periods in an attempt to gain better understanding of the behavior of the infection under the influence of antibiotic combinations. Attempts are presently under way to induce a similar type of experimental infection with other microorganisms, to widen the scope of therapeutic experimentation.

One unusual character of this infection is the apparently minor effect that the size of the infecting dose has on the final outcome. The average survival time varies but little, whether the inoculum contains 300 or 500,000 organisms. This probably indicates that additional bacteria in the inoculum do not augment the local lesion or hasten the dissemination provided some organisms are capable of initiating a local infection which persists in the muscle for 3 or 4 days prior to spread. The experiments reported here arbitrarily make use of an inoculum of 3000 to 5000 organisms. Whether larger or smaller inocula would affect the response to antibiotic therapy was not investigated.

Summary. A subacute *Streptococcus pyogenes* infection may be induced in mice by intramuscular inoculation which is useful in the study of combined antibiotic therapy. Synergism between penicillin and either streptomycin or bacitracin, and antagonism to penicillin action by either chloramphenicol or terramycin in long term treatment of this infection, are demonstrated.

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CHANGING CONCEPTS OF "XANTHOMATOUS BILIARY CIRRHOSIS"

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Thannhauser and Magendantz[25] in 1937 and Thannhauser in 1940[24] described a clinical syndrome as "xanthomatous biliary cirrhosis" in which they thought xanthomatous involvement of the large bile ducts and their partial obstruction to be the primary event which resulted later in this special type of biliary cirrhosis. MacMahon and Thannhauser[18] later revised this concept and suggested instead the term "pericholangitic biliary cirrhosis". More recently Ahrens and his associates[2] have separated cases of this disease into 2 types, 1) "primary biliary cirrhosis", which corresponds to the "pericholangitic biliary cirrhosis" of MacMahon and Thannhauser, and 2) "secondary biliary cirrhosis", the result of extrahepatic biliary tract obstruction. From the material presented in this paper, we believe that still another interpretation of the mechanisms involved in this disease is possible and suggest further revision for classification of cases that present the clinical picture originally described as "xanthomatous biliary cirrhosis".

Thannhauser and Magendantz[25] considered the disease to be characterized by: 1) skin xanthomata of the plain and tuberous variety, 2) enlarged liver and spleen, 3) obstructive type of jaundice with a duration of years, 4) extremely high value for total serum cholesterol and for lecithin, and 5) blood serum that is transparent and not creamy, despite the marked increase in cholesterol and lecithin, with low values for neutral fat.

In their publication, these authors, based on autopsy reports of Moxon and Fagge and of Pye-Smith 65 years earlier, suggested that xanthoma formation of the large bile ducts producing xanthomatous scar tissue may be the cause of the clinical syndrome described as xanthomatous biliary cirrhosis. It was their opinion that the development of xanthomata of the skin as well as the formation of xanthoma in the lining of the bile ducts were the expression of a systemic disease characterized by an increased new formation of cholesterol and hypercholesterolemia (hypercholesterolemic xanthomatosis). This xanthomatous involvement of the large bile ducts and their partial obstruction they thought to be the primary event which resulted later in this special type of biliary cirrhosis.

In 1949 MacMahon and Thannhauser[18], from an experience with 4 liver biopsies and 3 autopsies in patients presenting the clinical syndrome of "xanthomatous biliary cirrhosis", altered the opinion expressed by Thannhauser and Magendantz[25]. They report that the anatomical findings in the biopsies at the time when the extremely high cholesterol and lecithin values are present in the serum are: a) a non-specific, chronic inflammatory reaction centered about the smallest bile ducts and junctional ducts in the

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portal areas; b) blocking of the finest bile ducts and subsequent intralobular bile stasis; c) a lack of involvement of large bile ducts; and d) an absence of foam cells in the liver tissue.

In a discussion of the etiology of the disease, MacMahon and Thannhauser[18] suggest 2 possibilities that may be responsible for the clinical features of the syndrome: 1) that the excessively high content of serum cholesterol and lecithin may be caused only by retention resulting from obstruction of the finest bile capillaries and junction ducts; and 2) an increased new formation of cholesterol and lecithin by the liver together with impaired excretion which results from the obliteration of these ducts. They conclude that various laboratory findings and clinical features of the described cases favor the second hypothesis and propose the anatomical designation of "pericholangiolitic biliary cirrhosis with plain and tuberous skin xanthoma" for the syndrome and express the opinion that it is a liver disorder and a disease entity by itself.

Ahrens and his associates[2], after exhaustive clinical and pathological investigations of this disease, conclude that "xanthomatous biliary cirrhosis" belongs to a category of liver disease which they have called biliary cirrhosis, and they further divide this entity into 2 types. The first, primary cirrhosis, they associate with a type of intrahepatic obstruction of the finest bile canaliculi; and the second, or secondary biliary cirrhosis, is the variety which occurs upon extrahepatic obstruction of the bile ducts. In this definition, biliary cirrhosis is a syndrome consisting of prolonged jaundice and pruritus, enlarged liver, and only minimal signs of parenchymal damage. Xanthoma may or may not occur, but since the disease is characterized by hyperlipidemia that is often marked, they have been able to correlate the appearance and the severity of the xanthomata with the serum lipid-levels, striking examples being associated with levels of 1800 mg. per 100 cc. or more. They conclude that primary biliary cirrhosis can occur as a result of any number of noxious influences. For the body of this report we will continue to use the terminology proposed by Ahrens and his associates[2].

A series of cases has been collected by one of us (H.S.) over the past years, which illustrate the 2 types of syndrome; and the pathological material obtained from 2 of the cases helps further to clarify some of the issues about which there has been considerable confusion. Table 1 presents 2 cases of primary biliary cirrhosis with xanthomatosis (H.W. and C.T.), 1 case of secondary biliary cirrhosis with xanthomatosis (H.G.), 3 cases of extrahepatic biliary obstruction without xanthomata (M.K., W.G., and W.B.), and 1 case of infectious hepatitis (B.M.) with hyperlipidemia but no xanthomata.

That extra-hepatic biliary obstruction alone, in a patient with normal flocculation tests and a very high serum alkaline phosphatase, can produce serum lipid values that are practically identical with those which may occur in "primary biliary cirrhosis with xanthomatosis" is seen upon comparing cases M.K., H.W., and C.T. in Table 1. That this similarity may extend even to the presence of xanthomatous lesions is exemplified in patient H.G. (Table 1) who had an obstructive biliary cirrhosis of approximately 3 years' duration, following what appears to have been an injury to the common duct at the time of a subtotal gastrectomy, since jaundice first developed a few days after the operation. When the patient was seen 3 years after operation, during

TABLE 1.—LIVER FUNCTION AND SERUM LIPID VALUES IN SEVERAL TYPES OF JAUNDICE

Patient	Serum Bilirubin, mg. 100 cc.			Ceph. Chol.	Coll. Gold	Thymol Turbidity		γ Glob.	Alk. P'tase	Serum Lipids						Diagnosis*
	1 Min.	30 Min.	Total			Units	18 Hr. Ratio %			Cholesterol Total	Cholesterol Esters	E/T	Phospho. Lipids	Neutral Fat	Total Lipids	
H. W. ♀	6.94	3.86	14.0	+2	+3	9.9	78	—	86.4	1600	284	18	2500	1182	5470	Xanthomatous Biliary cirrhosis
C. T. ♀	0.73	0.58	2.06	+4	+4	17.6	33	29.1	80.0	1380	175	13	2900	429	4826	Xanthomatous Biliary cirrhosis
H. G. ♂	4.94	3.69	12.0	0		2.7	111	1.3	88.5	956	198	21	1995	172	3255	Obstructive Biliary cirrhosis
M. K. ♀	16.9	10.2	37.7	0	0	2.5	124	—	118.0	1158	98	8	2650	753	4625	Carcinoma Head of pancreas
W. G. ♂	12.8	10.2	34.5	—	—	—	—	—	—	365	99	27	585	251	1267	Carcinoma Head of pancreas
W. B. ♂	8.65	5.95	19.5	0	0	2.2	86	1.1	42.7	423	100	24	828	351	1669	Carcinoma Body of pancreas
B. M. ♀	1.07	0.83	3.52	+4	+2	20.2	6	10.8	33.3	595	212	36	1120	267	2123	Infectious hepatitis

TABLE 2.—LIVER FUNCTION AND SERUM LIPID VALUES IN CARCINOMA OF HEAD OF PANCREAS

M. K. ♀ Date	Serum Bilirubin, mg. 100 cc.			Ceph. Chol.	Coll. Gold	Thymol Turbidity		Alk. P'tase	Serum Lipids						Diagnosis
	1 Min.	30 Min.	Total			Units	18 Hr. Ratio %		Cholesterol Total	Cholesterol Esters	E/T	Phospho. Lipids	Neutral Fat	Total Lipids	
10-27-'47	15.3	9.50	32.0	+1	0	1.9	121	119.0	1096	115	11	2278	789	4236	
11-3-'47	16.9	10.2	37.7	0	0	2.5	124	118.0	1158	98	8	2650	753	4625	
11-3-'47					Operation					Cholecystgastrostomy					
11-6-'47	7.00	5.40	17.8	+1	0	1.1	136	71.6	857	103	12	1500	603	3029	Carcinoma, Head of Pancreas
11-10-'47	3.81	3.21	10.5	0	0	1.3	115	74.4	762	309	41	1042	266	2276	
11-14-'47	2.50	2.49	6.98	0	0	1.3	108	69.7	653	403	62	570	501	1993	
12-4-'47	1.19	0.57	2.56	0	0	0.7	128	24.3	310	168	54	270	246	938	

TABLE 3.—LIVER FUNCTION AND SERUM LIPID VALUES IN CASE OF XANTHOMATOUS BILIARY CIRRHOSIS

H. W. ♀ Date	Serum Bilirubin, mg. 100 cc. 1 Min.	30 Min.	Total	Ceph. Chol.	Coll. Gold	Thymol Turbidity Units	18 Hr. Ratio %	γ Glob.	Alk. P'tase	Serum Lipids: Cholesterol Total	Esters	E/T	Phospho. Lipids	Neutral Fat	Total Lipids	Diagnosis
11-25-'47	6.94	3.86	14.0	+2	+3	9.9	78	—	86.4	1600	284	18	2500	1182	5470	
2-2-'48	4.01	3.04	9.50	+2	+3	9.6	108	—	84.1	1985	282	14	4000	790	6763	
2-20-'48	3.57	1.34	6.91	0	+3	8.4	75	—	89.8	1510	222	15	3220	256	5134	Xanthomatous Biliary Cirrhosis
3-4-'49	3.66	2.17	7.73	+2	+3	13.0	21	15.9	78.0	1290	358	28	2372	191	4091	
5-3-'50	3.28	2.81	8.30	+1	+4	34.8	12	23.7	60.6	921	112	12	1448	266	2710	

TABLE 4.—LIVER FUNCTION AND SERUM LIPID VALUES IN CASE OF XANTHOMATOUS BILIARY CIRRHOSIS

C.T. ♀ Date	Serum Bilirubin, mg, 100 cc. 1 Min.	30 Min.	Total	Ceph. Chol.	Coll. Gold	Thymol Turbidity Units	18 Hr. Ratio %	γ Glob.	Alk. P'tase	Serum Lipids: Cholesterol Total	Esters	E/T	Phospho. Lipids	Neutral Fat	Total Lipids	Diagnosis
11-29-'48	0.73	0.58	2.06	+4	+4	17.6	33	29.1	80.0	1380	175	13	2900	429	4826	
12-2-'48	0.92	0.54	2.13	+4	+3	17.8	6	35.4	82.7	1284	288	22	2250	164	3890	
12-9-'48	0.85	0.65	2.38	+3	+4	18.9	11	35.8	94.1	1112	316	28	1910	0	3232	Xanthomatous Biliary Cirrhosis
1-25-'49	0.71	0.51	2.06	+3	+4	27.0	7	34.6	74.1	1146	141	12	2293	69	3692	
4-5-'49	0.76	0.56	2.25	+4	+4	30.2	7	35.2	57.4	1170	154	13	2055	315	2643	
10-11-'49	1.20	0.98	3.24	+4	+4	21.4	16	29.6	54.4	1225	138	11	2285	298	3900	

which time he had been constantly jaundiced, he had many skin xanthomata. Note the similarity of the results of the serum lipid studies, as well as the serum alkaline phosphatase level, in this patient to those of patient C.T., Tables 1 and 4.

A low cholesterol:ester ratio is generally accepted as an indication of diffuse liver cell damage. In a patient with a very high total cholesterol, another mechanism may perhaps be invoked, namely, an overloading of the esterification mechanism of the liver. Ordinarily, when serum cholesterol rises as the result of uncomplicated obstruction of the biliary tract, esterification of cholesterol by the liver is increased to a degree which maintains the ratio of esterified to total cholesterol within normal limits. In patient M.K. (Table 2), however, the low ester ratio must be interpreted as due to impaired esterification, since the absolute figure for cholesterol esters would be low even if the total cholesterol figure were within normal limits. It has been our experience that lowered cholesterol esters will often be the first sign of diffuse liver cell impairment when that impairment is secondary to long standing uncomplicated biliary obstruction. The relatively rapid decrease in blood lipids in patient M.K., following a short-circuiting of the bile flow above the obstruction, shows that uncomplicated biliary tract obstruction can result in a serum lipid profile that is not essentially different from one that occurs in primary biliary cirrhosis with xanthomatosis (Tables 2, 3, and 4). The rapid recovery of the esterification mechanism in the liver after the re-establishment of bile flow from the biliary tract is shown by the rapid rise in serum cholesterol esters at 7 and 11 days after cholecystgastrostomy was performed (Table 2).

The same degree of obstruction for a similar length of time does not always produce similar changes in serum lipids. Coincidentally, with the admission of patient M.K., another patient, W.G. (Table 1), with carcinoma of the head of the pancreas was admitted to Temple University Hospital with a history of jaundice of almost 4 months' duration, a period of jaundice identical with that of patient M.K. Serum bilirubin fractionations, flocculation tests, and the nutritional states of both of these patients were practically identical preoperatively. The values obtained by fractionation of the serum lipids, however, were strikingly different. Still another case of carcinoma of the pancreas with jaundice of only 3 weeks' duration and a total serum bilirubin of 19.5 mg./100 cc. (W.B., Table 1) already showed lipid elevations considerably higher than those of patient W.G. (Table 1) in whom the duration and severity of the jaundice were much greater. Again the liver function tests for evidence of diffuse liver impairment were negative, except for a low cholesterol:ester ratio. Furthermore, only 9 days previously, patients W.B. and W.G. showed no differences in their serum lipid values. The marked difference in serum lipid concentrations of patients M.K. and W.G., in whom the disease and the duration and severity of obstructive jaundice appeared to be so nearly identical, and the greater tendency of serum lipids to rise in patient W.B. as compared with patient W.G. (Table 1), even though the obstructive jaundice in the former was much shorter in duration and much less marked in severity, are puzzling and contradictory facts, and suggest differences in the efficiency of the cholesterol excretory mechanism.

The 2 important avenues for the excretion of cholesterol are the biliary

tract and the intestine. Bürger and Oeter[8] obtained indirect evidence for the direct transport of cholesterol into the intestinal lumen. They found the sterol content of the sigmoid to be almost double that of the duodenum and ileum. The colon, therefore, probably serves as the pathway for a large portion of excreted cholesterol.

The prevention of an accumulation of cholesterol in the blood in the presence of normal or abnormal synthesis could therefore be envisaged as dependent, in part, on normal excretory mechanisms. With the development of biliary obstruction, one of these excretory pathways is lost. However, given a normal intestinal excretion of cholesterol, this pathway of the sterol excretory mechanism may be able to "carry the additional load" satisfactorily and so prevent too marked an elevation of blood cholesterol, a set of conditions which we might postulate occurred in patient W. G. (Table 1). However, should the intestinal excretory mechanism for cholesterol be inadequate to cope with the extra load which results from biliary tract obstruction, then more marked retention of cholesterol occurs, with its accumulation in the blood to high levels as seen in patient M. K. (Table 1).

Striking elevations of serum cholesterol and phospholipids may result, therefore, from biliary tract obstruction alone, but, we postulate, only when the intestinal excretory mechanism for lipids is inadequate or impaired. Under such circumstances a serum lipid picture very similar to that found in primary biliary cirrhosis with xanthomatosis may develop. Furthermore, such patients (for example, H. G.) may form xanthomatous skin lesions, depending on the absolute level of lipid concentration reached and the duration maintained, as shown by Ahrens and his associates[2].

High level of serum cholesterol resulting from another type of liver disease is seen in patient B. M. (Table 1), in whom an increase in cholesterol formation and concomitant lag in esterification occurred during the course of infectious hepatitis. It would seem, therefore, that increased cholesterol production and/or decreased effective excretion may result from various insults to the liver, but it must be emphasized again that the various hepatotoxic influences (infection, inflammation, chemicals) as well as extra-hepatic obstruction, may each cause the clinical triad of jaundice, elevated serum cholesterol, an xanthomata.

Pathologic Anatomy. Unfortunately we were able to procure liver tissue or slides of liver tissue on only 3 of the cases presented. A needle biopsy of the liver of patient C. T. showed a fibrosis suggestive of that seen in portal cirrhosis, with no evidence of bile stasis. The specimen was too small for extensive study.

No gross liver tissue was available on patient H.W., but a microscopic section of liver stained with hematoxylin and eosin showed a pathologic lesion similar to those reported by MacMahon and Thannhauser[17,18] and later by Ahrens *et al.*[2]. The pattern of interlobular fibrosis resembled closely that described in portal cirrhosis, except that medium-sized bile ducts were difficult to find, and there was no evidence of bile duct proliferation. Large numbers of lymphocytes grouped in follicle-like clusters were present at scattered points in the fibrous stroma, and the finest bile canaliculi were often plugged with bile (Fig. 1a). The hepatic cells showed no evidence of necrosis, but often contained fine vacuoles. No material was available for fat staining. Large phagocytes containing a golden, finely granular pigment were

present in lymphatic and tissue spaces of most of the portal areas. There was no evidence of lymphatic distention (Fig. 1b).

Patient H.G. came to necropsy at another hospital and we were able to secure only a stained slide of liver and several pieces of formalin-fixed liver tissue. The formalin-fixed tissue was bile-stained, and there was one piece with a thickened fibrous border, presumably a fibrous thickening of Glisson's capsule. Microscopically, sections of this tissue stained with hematoxylin and eosin revealed a completely necrotic parenchyma with extensive disarrangement of the architecture, so that no canalicular or sinusoidal patterns could be detected. The portal areas were in a fair state of preservation, however, and in these, as well as in the thickened capsule, extensive bile-duct proliferation was present. Several large bile ducts were sur-

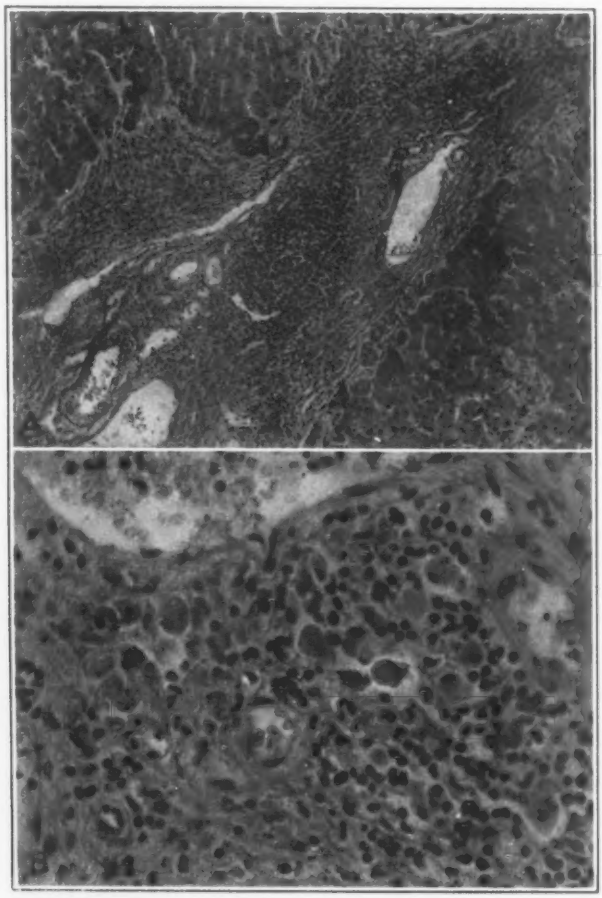

FIG. 1 (A)—Section of liver from case of primary biliary cirrhosis with xanthomatosis. Note focal collection of round cells in the fibrous tissue and plugged bile canaliculi in the parenchyma. (B)—Higher magnification of same tissue demonstrating phagocytes in portal areas. These phagocytes contain a powdery golden pigment which the photograph does not demonstrate.

rounded by a vacuolated matrix, in which no definite cell boundaries could be established due to the extensive fragmentation of the residual stroma. Sudan IV stains on material prepared by the freezing method, however, demonstrated large amounts of fat in these spaces. Fragments of desquamated columnar epithelium, found either in the lumen or attached to small portions of the wall of the space, established the structure as a bile duct (Fig. 2 a, b and c). Immediately peripheral to this "xanthomatous" bile duct, were several dilated lymph channels engorged with large phagocytes, some of which contained bile pigment in coarse granular form. Sudan IV stains demonstrated large numbers of fat-filled phagocytes lying either in dilated lymphatics or in edematous tissue spaces, in the stroma immediately surrounding this bile duct. Sudan IV stains also showed similar changes elsewhere in the thickened capsule.

Discussion. Until Ahrens and his group[2] separated so-called xanthomatous biliary cirrhosis into 2 groups, the primary and secondary, on the basis of intrahepatic and extra-hepatic obstruction respectively, no clear indication of the existence of 2 clinical entities had been made. As we have indicated, a separation of the 2 varieties of the disease may be made by laboratory tests and can be established by pathological studies; and it is, therefore, probable that 2 different pathogenetic processes, acting through fundamentally different mechanisms, can produce the same end results of jaundice, elevated serum cholesterol and xanthomata.

Thannhauser and Magendantz[25] originally believed that xanthomata of the skin as well as xanthoma formation under the lining cells of the bile ducts were results of a systemic disease, and that the bile-duct xanthomata caused an obstruction and an obstructive type of cirrhosis. More recently, MacMahon and Thannhauser reversed this concept and described an intrahepatic obstructive lesion, as the result of an inflammatory process, which they believed predisposed to the hypercholesterolemia.

The question of xanthomata in the bile ducts has caused considerable confusion, due probably to the relative frequency with which these were reported until the turn of the century and their almost complete disappearance from the literature since. We have found only 1 case reported since 1903[26] other than the one (H.G.) that we are presenting in this paper.

In 1851 Addison and Gull[1] reported 5 cases of what they termed vitiligoidea, today known as xanthomata of the skin. In 3 of the 5 cases there was associated jaundice and it was not until 1868 that Fagge[9] reported 2 cases in which there was no clinical evidence of extrahepatic obstruction. In the first case, a 33-year old male, jaundiced for 2 years, developed xanthomata of the eyelids. The liver was enlarged and tender; the urine contained bile and the stool was normal in color. The patient had contracted syphilis 11 years before admission, and for the previous 5 years had had occasional hemoptysis. The second case was in a female, who developed jaundice ascribed to "fright" after the death of one of her children. She developed xanthomata and an enlarged liver, but had normal color stools. Fagge then notes that the xanthomata are associated with a jaundice that is independent of obstruction of the biliary tract. In 1869 Murchison[20] described a case of jaundice in an inveterate drinker, who subsequently developed xanthomata. There was no evidence of obstruction, and the microscopic description of the liver resembles that

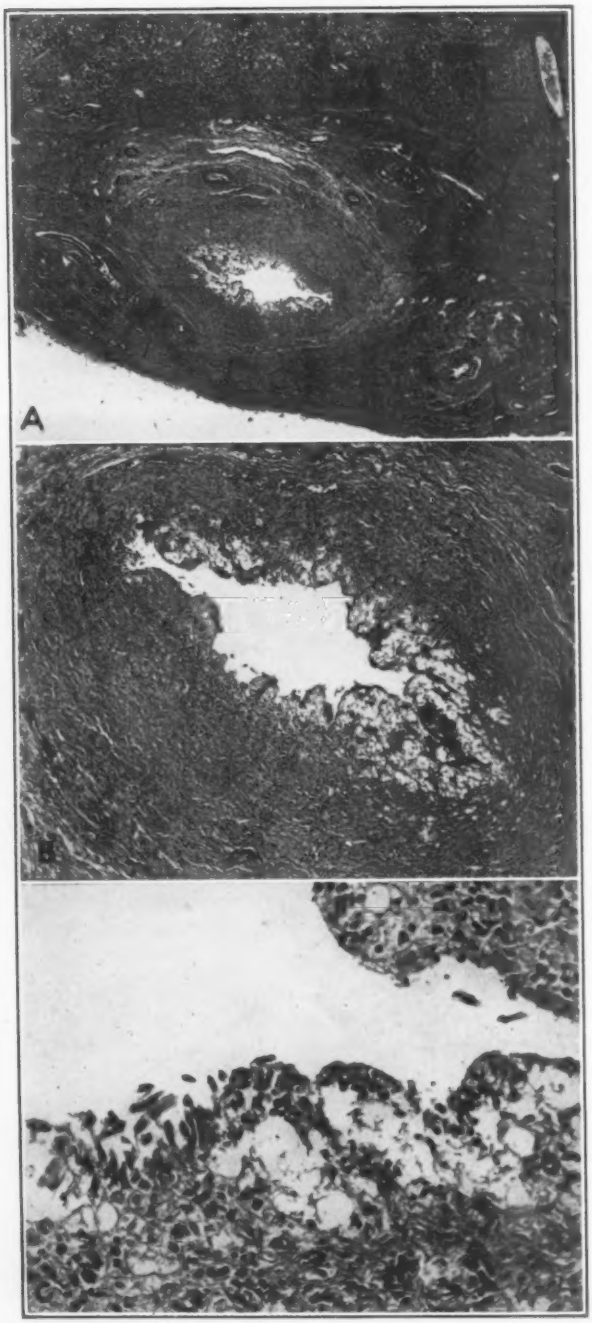

FIG. 2 (A)—Xanthoma cells lining a hypertrophied bile duct found in the thickened capsule of the liver of patient H. G. (x 35). (B)—Higher magnification (x 50). (C)—Higher magnification (x 200) of wall of bile duct demonstrated in A and B. Xanthoma spaces stained deep orange with Sudan IV. Note denuding bile duct epithelium.

depicted by MacMahon and Thannhauser.

Four years afterward, Moxon[19] recorded a case of obstructive jaundice of long duration in which a 32-year old male developed widespread xanthomata. Liver tissue obtained at autopsy showed xanthomata of bile ducts. The cause of the obstruction in this case was a fibrous scar binding the hepatic duct at its bifurcation so that only the finest probe could be forced through. Here again the question as to etiology arises, and Moxon[19] states, "This case offers several points of interest; not the least of these is the fact that it is the first case which clearly showed xanthelasma to be the sequence of chronic jaundice, and not, as we supposed, a special cachexia involving the liver and skin in some special disorder." Apparently Moxon was disturbed by the same conflicts that we enjoy today concerning this

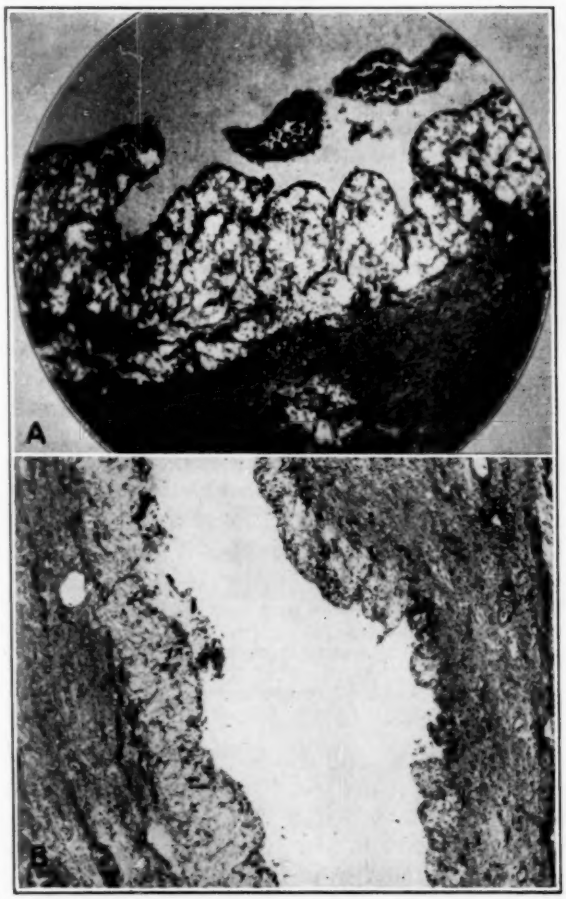

FIG. 3 (A)—Xanthoma of gallbladder (x 100) and (B) of bile duct (x 50) from case reported by Weidman and Boston[26].

disease. In that same year, in 1873, Pye-Smith[22] described a case of jaundice associated with xanthomata in which a clinical diagnosis of obstruction due to gall stones had been made. At necropsy dilated xanthomatous bile ducts were found and Pye-Smith recorded, "The patches in the ducts looked just like atheromata in an artery, with which condition indeed they correspond histologically."

troubles as secondary to the development of xanthomata in the viscera.

With the exception of the case of Weidman and Boston[26] reported in 1937, we were unable to find other reports of xanthomata in bile ducts after 1905. The case recorded by Weidman and Boston is of interest in that it is the first one published which contains photographs of gallbladder xanthoma (Fig. 3a), and Fig. 3b demonstrates

TABLE 5.—CASES IN WHICH XANTHOMA HAVE BEEN FOUND IN BILE DUCTS

Author	*Date*	*Clinical Diagnosis*	*Autopsy Diagnosis (Liver)*
Moxon[19]	1873	Cutaneous xanthomata Obstructive jaundice	Fibrous scar at junction of right and left hepatic ducts Dilated bile ducts Xanthoma in bile ducts
Pye-Smith[22]	1873	Cutaneous xanthomata Jaundice due to gall stones	Dilated bile ducts Xanthoma in bile ducts
Futcher[10]	1905	Cutaneous xanthomata Jaundice due to biliary obstruction	Stones in common and hepatic ducts Xanthoma of large bile ducts
Weidman and Boston[26]	1937	Cutaneous xanthomata Hypertrophic biliary cirrhosis Herpes zoster, syphilis	Hypertrophic biliary cirrhosis Carcinoma of ampulla Xanthoma of gallbladder Xanthoma of large bile ducts
Shay and Harris*	1951	Postoperative stricture of common duct Jaundice Cutaneous xanthomata	Hypertrophic biliary cirrhosis Xanthoma of large bile ducts

* Present series

The next report in which xanthomata of the bile ducts were found was made by Futcher[10], who described 3 cases of jaundice associated with xanthelasma, 2 with, and 1 without extrahepatic obstruction. In one of those with the extrahepatic obstruction, stones were present in the hepatic ducts, and "On section of the liver the bile ducts stood out everywhere looking like sclerotic arteries." The microscopic examinations revealed xanthoma cells in the bile duct wall. Futcher then states that Besnier, Hollopeau, and Kaposi regarded the jaundice and liver

a bile-duct xanthoma found in the same case. The patient had long-standing jaundice due to carcinoma of the ampulla, and cutaneous xanthomata completed the picture. Here we must take issue with Thannhauser and Magendantz[25] when they state, in citing this case, that the carcinoma of the ampulla had nothing to do with the rest of the syndrome and clinical findings; for it is unquestionable that, as the cause of the extrahepatic obstruction, it was responsible for the rest of the syndrome.

Listed in Table 5 are the cases found in the literature in which bile duct xanthomata are described, and it should be noted that in all of these cases there was extrahepatic biliary obstruction. These, plus the case of H.G. reported in this paper, show that xanthomata in the large bile ducts are the result of long standing jaundice due to prolonged extrahepatic obstruction with complicating hypercholsterolemia. Bile duct xanthomata do not occur in the so-called primary biliary cirrhosis with xanthomatosis.

In order to derive a feasible relationship between long-standing obstruction, high serum cholesterol, and bile-duct xanthomata, we were guided by the striking similarity of the bile-duct xanthomata to atherosclerosis in blood vessels. There has been more than suggestive evidence in the literature that inbibition of lipids from the blood stream by the vessel intima occurs[3,15,16,21]. In a series of experiments, Hueper[15] showed that the arterial intima would imbibe the large molecules of polyvinyl alcohols and other macromolecular carbohydrates. These experiments lent credence to the imbibition theories of Virchow, as stated by Leary[16] and Page[21] and of Anitschkow[3]. More recently, Gofman[12] has shown that there is excellent correlation between arteriosclerosis and the blood serum level of a large cholesterol–protein complex, thus establishing that the cholesterol in serum is often bound to a large molecule at the time when the intimal lesion is forming. Finally, Buck and Rossiter[7] have suggested that the presence of fat in the media of an artery is related to aging, in contradistinction to the presence of large amounts of intimal fat which they correlate with atherosclerosis.

If, therefore, there is a strong possibility that the arterial intima can imbibe large molecule complexes with which lipid may be combined, cannot then the musoca of a bile duct carry on that same function under certain circumstances? Boyd[6] suggested this mechanism in cholesterolosis of the gallbladder, and a similar mechanism may operate in a bile duct. It has been emphasized repeatedly[21] that atherosclerosis of an artery occurs at pressure points and that certainly a marked increase of intraluminal pressure occurs in the bile ducts as a result of extrahepatic obstruction. Given, therefore, a patient with extrahepatic obstruction, in whom the intestinal excretory mechanism for cholesterol is not able to take on the additional excretory load, a marked rise in blood cholesterol will occur; this elevation in the blood may in turn increase the concentration of cholesterol in the bile where, under the increased pressure in the duct system (the result of the obstruction), imbibition of cholesterol by the duct mucosa and the formation of xanthomata can in time result. It is possible that a third factor, namely embarrassment of lymphatic drainage from the liver, would enhance the rate of xanthoma formation.

Insofar as primary biliary cirrhosis with xanthomatosis is concerned, we believe that the elevation of the blood cholesterol is a cardinal factor and that the liver fibrosis follows this metabolic change; a change that is, in turn, dependent on a preceding diffuse type of hepatocellular damage of unknown etiology. Some investigators do not emphasize the role of the lipid in the fibrosis[2,18] but instead stress the marked chronic inflammatory reaction that is uniformly present in the stroma. Leary[16], however, believes that crystalline cholesterol esters, when they block periportal lymphatics as was demonstrated for silica[11,13], are a stimulant to the growth of fibrous tissue.

Such a mechanism could adequately explain this fundamental histological finding in the liver tissue common to all the cases of primary biliary cirrhosis with xanthomatosis.

Although it is not completely proven that circulating bile salts are the sole cause of itching in jaundice, it is generally accepted that they play an important part in the production of this symptom. The prominence of itching as an early and often severe symptom of this disease lends support to the "overproduction" concept of sterols by the liver as an early manifestation of the disease, and accounts for the itching through an overproduction of bile salts, and for the hypercholesteremia by an overproduction of cholesterol. At this stage the hypercholesteremia, in accordance with Leary's view, can supply the necessary irritant that stimulates the production of fibrous tissue around the finer cholangioles resulting in the periportal fibrosis emphasized by MacMahon and Thannhauser in their current concept of the "early pathology in the liver" in this disease. Such a sequence, in our opinion, puts periportal fibrosis in a secondary and not a primary role. Following this, no severe obstruction in the biliary tract and no marked increase in pressure in the biliary tree occurs. In these patients, therefore, no xanthomata of the larger bile ducts develop.

We have already seen that liver damage produced by various hepatoxic agents can produce elevated blood-cholesterol levels, and these have been emphasized by the recent reports of Hanger and Gutman[14], Stolzer *et al.*[23], and Bockus and Monaghan[5], implicating arsenic, and that of Bevans and Batchelor[4], who suggest that neocinchophen may have exerted a delayed deleterious effect.

Summary and Conclusions. We agree that the concept of "xanthomatous biliary cirrhosis" as originally conceived by Thannhauser and Magendantz[25], relating the clinical and biochemical picture of the disease to the presence of xanthomata of the large bile ducts, must be rejected. This Thannhauser himself has done[18]. MacMahon and Thannhauser[18] have more recently substituted the term "pericholangiolitic biliary cirrhosis with plain and tuberous skin xanthoma" for this disease. We are in complete accord with these authors that the disease described by them is a liver disorder and a disease entity, and that an overproduction of cholesterol and also of other sterols (bile salts) by the liver constitutes an important facet of this disease. They fail, however, to recognize that hepatotoxic agents (arsenic, cinchophen, viruses) other than that or those concerned in the idiopathic variety of the disease, as well as extrahepatic obstructive jaundice with hypercholesteremia of long enough duration, can produce the clinical and biochemical picture that may be indistinguishable from the idiopathic form.

Ahrens and his associates[2] recognized that extrahepatic biliary obstruction could produce such a clinical picture and divided their cases into "primary biliary cirrhosis" which corresponds to the "pericholangiolitic biliary cirrhosis" of MacMahon and Thannhauser and "secondary biliary cirrhosis" resulting from extrahepatic biliary tract obstruction. We cannot accept this classification fully because we do not believe that the disease they classified as "primary biliary cirrhosis" (a disease which appears so predominantly in adult women; has itching as a prominent symptom which often appears for some time before recognizable jaundice; shows a marked

elevation in serum cholesterol and phospholipids; and produces skin xanthomata depending on the degree and duration of the hypercholesteremia) has its "pathogenesis in some manner initiated by prolonged biliary obstruction"[2]. We do not classify this disease primarily as a biliary cirrhosis and believe from our studies that it is initiated by hepatocellular disease which first induces an increased production of sterols and phospholipids by the liver.

On the basis of our studies, we suggest that the "pericholangiolitic biliary cirrhosis" of MacMahon and Thannhauser[18] and the "primary biliary cirrhosis of Ahrens and his associates[2] would be more adequately described from an etiologic, biochemical, and primary pathologic standpoint under the term of "Hepatocellular Hypercholesterolemic Cirrhosis." We would recognize under this term a disease produced primarily by hepatotoxic agents. One group under this classification is the idiopathic variety, in which the hepatotoxic agent or agents are unknown, and which appears to be importantly sex-linked; another group comprises those cases in which the hepatotoxic agents may be recognizable, such as arsenic, viruses, or cinchophen. Patients in either group may or may not develop skin xanthomata, depending on the level and duration of the hypercholesterolemia, but do not develop xanthomata of the larger bile ducts at any time.

A second variety in which the clinical and serum lipid picture may be indistinguishable from the above groups, but in which the primary mechanism producing the disease is very different, is presented by those patients in whom extrahepatic biliary obstruction initiated the disturbance. These patients may develop not only skin xanthomata depending upon the factors already mentioned but may, in addition, develop xanthomata of the larger bile ducts or even the gallbladder. This group is the only one in which the process is essentially and primarily a biliary cirrhosis.

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A REVIEW OF THE LITERATURE ON PREOPERATIVE PROPHYLAXIS OF THE BOWEL WITH ANTIBACTERIAL AGENTS

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THE potentially pathogenic intestinal organisms offer a serious threat in all gastrointestinal surgery, and the value of antibacterial agents in preparing the bowel for surgery is widely acclaimed by some as the greatest recent advance. However, it is repeatedly emphasized that these drugs must be used as adjuvants to, and not as substitutes for, good surgical technique. Until recent years no agent had affected the intestinal microflora profoundly and consistently without local or systemic toxic effects. Early attempts at intestinal antisepsis, beginning as far back as 1887, made use of such substances as charcoal, naptholene, iodoform, chlorine, and salicylates; and as the results were disappointing, little or no attempt was made to use these to prepare the gastrointestinal tract for surgery. New hope to achieve intestinal disinfection came with the introduction of the sulfonamides and the antibiotics.

Sulfonamides. Sulfanilamide was first prepared in 1908[36] but it was not until 1935 that reports were made by Domagk[20] and by Trefouel[90] attesting to its efficacy in bacterial infections. Although many species of medically important bacteria are in some degree susceptible to one or other of the sulfonamide drugs, some strains are inherently insensitive while others may acquire resistance through exposure to the drug. It has also been shown that organisms which are not sensitive to the sulfonamides may prevent the drug from acting upon a sensitive strain, both in the test tube and in the body.

Certain of the sulfonamides, which are poorly absorbed from the intestine, show a high degree of antibacterial action localized to the bowel, even though these compounds possess but

slight intrinsic antibacterial activity *in vitro*. Sulfanilylguanidine (sulfaguanidine), originally synthesized by Robbin, Williams, Winnek, and English[79] (1940), was the first of these substances described, and in 1940, Marshall and his co-workers[53] showed that, although it is water soluble, it is poorly absorbed from the gastro intestinal tract, and therefore remains in sufficiently high concentrations to act as a local chemotherapeutic agent. It was noted that the concentration of coliform bacteria in the feces of mice was greatly reduced after oral administration of the drug. These observations seemed of possible significance for surgeons and led Firor and Jonas[33] (1941) to use sulfanilylguanidine in preoperative preparations, and the convalescence of 12 surgical patients studied gave the impression that the drug was a real adjuvant in colonic surgery. Further clinical experience the same year by Firor and Poth[34] modified the initial impression and made it evident that experimental work was necessary. Experimental and clinical studies with sulfanilylguanidine have shown that when an adequate amount of the drug is given at sufficiently frequent intervals, the coliform flora of the bowel can usually be significantly reduced from over 10,000,000 to less than 1,000 per gram of wet stool, which is made impressive when expressed as a reduction of 99.99%. The explanation which is offered for the greater effectiveness of the drug when administered frequently is that, by shortening the interval between doses, more constant contact is maintained between the drug and the mucous membrane harboring the bacteria. This treatment does not decrease the number of other bacteria in the colon.

No reduction in the number of coliform organisms was obtained in the presence of ulcerative lesions of the bowel, possibly due to an antisulfonamide factor, such as exists in purulent exudates, which renders this compound ineffective. In 1941, Vieta and Stevenson[91] also noted a marked reduction in number of coliform organisms in the bowel of 18 of 27 patients. The 9 failures to get significant reduction were ascribed to: presence of ulcerative lesions; infrequency of administration; presence of drug-resistant coliform strains. They also noted that sulfanilylguanidine, by depressing the coliforms, interfered with the synthesis or absorption of vitamin K in some patients, which would affect the plasma prothrombin level. They concluded that sulfanilylguanidine is not the ideal chemotherapeutic agent for intestinal antisepsis and that its practical application to bowel surgery is limited. The use of sulfanilylguanidine was discontinued at the Johns Hopkins Hospital[53] in 1940, despite the optimism generated by its early investigation, as it was found that approximately 50% is excreted in the urine as the conjugated acetyl derivative, which is inactive therapeutically, and can produce crystalline deposits in the kidney pelvis. In addition, this sulfonamide frequently produced drug reaction, and did not cause a significant alteration of the flora of the intestinal tract.

Edgar Poth[67] in 1940 outlined a plan by which it was hoped that a compound could be found which would possess the properties of an intestinal antiseptic. Ideally such a compound should be poorly absorbed from the gastrointestinal tract, non-irritating to the bowel, non-toxic, possessed of antibacterial activity, and maintained in the lumen of the bowel in high concentration. Subsequently, Poth and his associates[67,68,70] reported on a considerable series of conjugated sulfonamides which possessed bacteriostatic properties localized to the bowel. The

2 most promising of these were succinylsulfathiazole (sulfasuxidine), synthesized by Miller, Rock, and Moore[58], 1939, and phthalylsulfathiazole (sulfathalidine), synthesized by Moore and Miller[59], 1942. Phthalylsulfathiazole is apparently the most potent of the sulfonamides described to date as regards local antibacterial action in the bowel, and was found to be 2 to 4 times as effective as succinylsulfathiazole in causing a reduction of the coliform organisms in the gastrointestinal tract. Approximately 5% of the ingested dose of either drug is excreted in the urine, and the toxicity of both is practically the same at equal dosage levels. They are relatively non-toxic, but it is not unusual to encounter a moderate increase of temperature, anorexia, malaise, and headache, which, however, would not necessitate interruption of the therapy. Of the 2 drugs, phthalylsulfathiazole is probably the better, as twice as much succinylsulfathiazole must be used to give comparable reduction of the coliform organisms. The antibacterial action of these compounds effects a considerable reduction of the Gram-negative flora of the bowel. The coliform bacilli were used as an indicator of antibacterial action as they are moderately resistant to the sulfonamides and their cultural characteristics are such that they can be followed quantitatively quite simply. The coliform count, however, does not appear to be an adequate index of the effect of these drugs upon the total colonic bacterial population.

In their monograph on succinylsulfathiazole, Poth and Knotts[67] report that the drug given to patients on a low-residue diet in therapeutic doses (3 gm. every 4 hours) profoundly altered the feces and the latter became semi-fluid, small in bulk, and relatively odorless. It required from 3 to 7 days to produce significant reduction in the coliform count in 94% of the cases. Even after 5 weeks the number of coliform per gram of wet stool averaged less than 1,000 organisms, as compared to an average normal flora of about 10,000,000. Firor[32] showed that, although the aerobic fecal flora may be altered for periods as long as 6 weeks, succinylsulfathiazole had no appreciable effect on enterococci, *Pseudomonas* or *Proteus*. Poth[63] makes the assumption that the characteristic odor of feces is produced by the anaerobic streptococci and the *Bacteroides*, and that since this characteristic fecal odor disappears under succinylsulfathiazole therapy, these organisms must be profoundly affected by the drug. Experiments on the bacterial flora of rat feces by Miller[56] in 1945 showed that, although feeding succinylsulfathiazole and phthalylsulfathiazole caused a decrease in the coliform count, there was no significant change in the "total aerobes," "total anaerobes," or anaerobic spores in the feces.

Poth and Ross[70] reported experimental studies on phthalylsulfathiazole as an intestinal antiseptic. The dosage with this drug is 1.5 gm. every 4 hours, and the coliform flora shows a 99.99% reduction, but it is ineffective against the enterococci. Lockwood[51] demonstrated that the clostridia were reduced to significantly low numbers in the feces. The fecal odor is reduced, but more attention must be directed towards emptying of the bowel with enemas and purgatives, because the feces become rather tenacious and stringy, with a tendency to adhere to the bowel wall. Phthalylsulfathiazole could be more effective in the presence of diarrhea, and is suggested as the drug of choice during the postoperative period.

It should be remembered that the sulfonamides are bacteriostatic sub-

stances and that they do not ordinarily possess bactericidal properties. Therefore, it is required that these drugs come in contact with the entire mucosal surface to effect a significant alteration of the bacterial flora. A segment of the bowel into which no drug passes will continue to feed organisms into distal portions of bowel, and the feces will continue to show high bacterial counts. The time required to alter the bacterial flora in the presence of diverticulosis is prolonged.

Crystalluria has not been observed to follow the oral administration of succinylsulfathiazole or phthalylsulfathiazole unless the urine has an unusually strong acidity. The free form of the drugs is not excreted in large quantities, and the conjugated drug forms soluble salts at a pH of 5.6. It has been suggested that these 2 drugs interfere with the synthesis of an antihemorrhagic factor, probably Vitamin K, but this is not marked as with sulfanilylguanidine.

Experimental evidence in dogs[71] revealed that succinylsulfathiazole and phthalylsulfathiazole favor the process of healing of the bowel at the line of suture. There was an unquestionable reduction of postoperative peritonitis, infection of abdominal wounds, and occurrence of fecal fistulae in treated patients. Allen[4] (1943) and Behrend[8] (1944) have remarked on the unusually smooth convalescence following use of these sulfonamides. The use of these drugs is contra-indicated in those cases in which complete obstruction is present, and they are also of lesser value if administration cannot be continued preoperatively for 1 week. Shaeffer and Pulaski[85] (1950) consider these non-absorbable sulfonamides in doses of 0.1 to 0.25 gm. per kilo. of body weight for 5 days to be reasonably effective, if it is possible to postpone operation for that length of time. They also point out that these are economical and usually readily available.

While succinylsulfathiazole and phthalylsulfathiazole have not proved a ready cure for chronic ulcerative colitis, certain claims have been made for them. Their use will frequently induce and maintain a remission, on occasions quite dramatic, and anal fistulae may heal. The drugs must be administered continuously in full therapeutic doses for months, and phthalylsulfathiazole is better tolerated and is probably the superior drug in this instance.

Penicillin. The recognition of penicillin as an antibacterial agent started with the experiments of Fleming in 1929, but not until Florey and his colleagues[1,14] overcame the difficulties in its purification and demonstrated its remarkable therapeutic powers, was its potential value in human medicine fully realized. It has a very low toxicity for the host, and has proved active against a great many Gram-positive aerobic and anaerobic bacteria. Enterococci and coliform bacteria are relatively insusceptible, yet it does possess some degree of antibacterial activity against both when given in large doses. It is bacteriostatic in low concentrations and appears to be bactericidal in high concentrations. Penicillin was never seriously considered in the role of a preoperative antiseptic for bowel surgery, because of the exceedingly large doses that would be required and the correspondingly large wastage that would occur. Oral administration is not favored, because penicillin is to some extent inactivated by the acidity of the stomach and by the penicillinase produced by bacteria in the gut. Griffin and his co-workers[38] recommend, however, that intramuscular penicillin be given prophylactically and postoperatively after every laparo-

tomy were contamination or infection might play a role.

Streptomycin and Dihydrostreptomycin. In the search for antibiotic substances which are more bacteriostatic or bactericidal for Gram-negative bacteria than penicillin, Waksman and his associates isolated two apparently related substances, streptothrycin[94] and streptomycin[92]. Of the two, streptomycin, obtained from a strain of *Streptomyces griseus*, is somewhat more active against Gram-negative bacilli and is less toxic for the host, is water-soluble, and is extremely stable in its passage through the body. Relatively very little transfer of streptomycin occurs between the blood and the lumen of the gastrointestinal tract in either direction, even with large doses. When streptomycin is given by mouth, numerous workers have shown that the drug is excreted almost entirely in the feces, and much of the ingested dose can be recovered, provided suitable extraction procedures are employed.

The mechanism by which streptomycin acts *in vivo* is not fully understood, but seems to result in the actual killing of the organisms. From observations *in vitro* it would appear that, under appropriate conditions, streptomycin can act as a bactericidal agent, although a few workers consider that its action is primarily bacteriostatic. Streptomycin is of great value in combatting Gram-negative intestinal organisms, such as *Escherichia coli* and *Aerobacter aerogenes*, and it is sometimes also effective against Gram-positive cocci, particularly non-hemolytic streptococci. Both *Pseudomonas aeruginosa* and *Proteus* are quite resistant to streptomycin and in addition have marked potentialities for acquiring augmented resistance to the drug. Anaerobic organisms, including *Clostridium* and *Bacteroides*, are quite resistant to the action of streptomycin. It has been suggested[11,35] that the resistance exhibited by anaerobic microorganisms may be the result of differences in metabolism, streptomycin effectively blocking enzyme systems essential to the growth of aerobic bacteria.

Resistance to streptomycin is achieved with great facility by most organisms both *in vitro* and *in vivo*. As strains become resistant, biochemical properties alter, giving evidence of damaged enzyme systems[84]. In 1948, Paine and Finland[62] and Miller[57] reported finding 2 types of variants from the same "sensitive" strain of several different organisms. Both of these variants were resistant; one could grow either in high concentrations of streptomycin or in its absence; the other grew only in the presence of streptomycin. The former is called the "resistant" variant, and the latter, the "dependent" variant. Inhibition of the development of drug resistance by a combination of streptomycin with sulfonamides and penicillin was shown to occur by Klein and Kimmelman[50] (1947). The added drug interfered with the rapid multiplication of the variants surviving the action of streptomycin, and thus modified the rate at which resistance developed.

Dihydrostreptomycin, discovered in 1946, is prepared by the catalytic hydrogenation of crystalline streptomycin-trihydrochloride, and this reduction has an action very similar to streptomycin itself[7,22,37]. It has an *in vitro* activity equal to that of streptomycin for some bacterial species, but for others its activity is only a fraction of that of streptomycin. Recognizing that more potent anti-bacterial agents than the sulfonamides should be advantageous in further reducing the bacterial flora of the colon, interest was aroused by reports of various workers

relative to the effect of oral streptomycin in experimental animals[26,61,81,86]. Since this substance was found to be effective against Gram-negative bacilli, was absorbed very poorly from the intestinal tract (some workers have reported recovering 95% in the feces), and therefore relatively non-toxic systemically, it was thought immediately that it might be a useful adjuvant in preparing the large bowel for surgery.

Preliminary reports in 1945 of the effectiveness of streptomycin in intestinal prophylaxis by Zintel *et al.*[98] were encouraging, showing a more rapid decrease in coliform organisms than when succinylsulfathiazole was used, and causing a virtual disappearance of enterococci. Reimann, Price, and Elias[76] found that oral streptomycin cleared the intestine temporarily of certain Gram-negative bacteria, giving an almost odorless stool. Drug-sensitive strains of *Escherichia coli*, *Salmonella typhosa*, and certain other bacteria were promptly suppressed or eliminated from the feces of typhoid patients studied, so long as an adequate amount of streptomycin is maintained. Cessation of treatment is followed by a rapid return of the flora, but they conclude that even a temporary suppression is of value at times, particularly during intestinal operations. There was evidence of a great variability in the resistance of different strains of *Escherichia coli* to streptomycin. Despite seemingly lethal concentrations of the antibiotic in the bowel lumen, resistant forms still developed and they thought this might be due to the presence of relatively inaccessible foci, such as the mucosal crypts of the colon.

Robinson[80], in commenting on the studies he and his co-workers made with mice, says, "Not only were the numbers of the coliform organisms rapidly and effectively reduced, but also the total flora was strikingly decreased." The results of this study suggested that streptomycin might be effective, not only as a chemotherapeutic agent for enteric diseases, but also as a form of preoperative and postoperative treatment in gastrointestinal surgery. Buggs *et al.*[13] found that the degree of resistance of bacteria *in vitro* was not a reliable guide to the exact amount needed to gain therapeutic effects in the body. Rapid development of resistant strains occurred in a few patients, resulting in failure of treatment. Zintel *et al.* [100], in a series of 15 patients receiving 1 gm. of streptomycin daily, reported a marked and sustained reduction in the numbers of the 3 groups of fecal organisms, studied: coliforms, enterococci, and clostridia. The patients were followed from 6 to 10 days after institution of streptomycin, and, even in the limited dosage employed, it was much more effective than succinylsulfathiazole, especially in regard to enterococci and clostridia. Kane and Foley[49] studied the effect of oral streptomycin on the fecal flora of 5 patients and found that *Escherichia coli* was eliminated from the stool within 2 days with a dose of 2 gm. per day, but this dose did not seem to affect the anaerobic flora of the stool and had no appreciable effect on the fecal streptococci.

Poth and his co-workers[54] cautioned that streptomycin given orally before surgery might produce deleterious effects by virtue of the marked reduction of the bacterial flora, particularly in the upper alimentary tract, thereby interfering with the absorption of certain fat-soluble substances, most important being vitamin K, resulting in an elevated prothrombin time. Lockwood *et al.*[52] determined prothrombin times by the Quick method every 2 to 4 days in 11 patients in their series, and in 7 of them there appeared to be a slight

prolongation, but no correlation was found between a rise in prothrombin time and a drop in bacterial flora. Another objection offered by Poth[54] was that in view of the rapid resistance to streptomycin, developed by the intestinal bacteria, one would be reducing the usefulness of the drug in the treatment of postoperative complications, should such develop.

It seemed possible that a combination of streptomycin and phthalylsulfathiazole might be more efficacious than streptomycin alone and might overcome reversion in count, as the 2 drugs have different antibacterial mechanisms, and the organisms which develop streptomycin resistance might be inhibited by the sulfathalidine, those resistant to both being rarely encountered. A contrary opinion was held by several groups of observers[52,54], and Rowe, Spaulding, Madajewski, and Bacon[5,83,88], conceding a value to the combined treatment, found reversion occurred in patients following prolonged administration of streptomycin, alone and combined with sulfathalidine, and invariably when a smaller dose of 0.5 gm. of streptomycin alone was given. The coliform count, with one exception, did reflect the "total" counts for a period up to 2 days, but after this time the counts diverged sharply and in no individual case could the number of coliform bacilli be taken as a reliable index of the total population. They concluded there was an irregular and temporary effect upon the "total" counts, and that the coliform count is not an adequate index of the effect upon the total bacterial population. Multiplication of streptomycin-resistant sulfathalidine-susceptible organisms was observed on several occasions in spite of the fact that sulfathalidine was being administered at the time, but the number of such variants was seen to decline over a period of 1 to 3 days. They concluded that, since bacteria develop resistance to streptomycin even in the presence of phthalylsulfathiazole, it does not appear advisable to administer streptomycin for more than 2 days before an operative procedure upon the large bowel, in addition to a regimen of phthalylsulfathiazole for 7 days previous to the operation.

At the present time, the advisability of administering streptomycin orally before operative procedure upon the large bowel is a controversial subject, to say the least of it. Zintel, Wiley, Nichols, and Rhoads[100], Morton and Smith[60], and Herfort and Standard[41] report favorable clinical results, although, in the latter study, concomitant with the decreased bacterial counts, there appeared a significant elevation in prothrombin times of both whole and diluted plasma specimens. However, once the remaining bacteria became drug-fast, the synthesis of vitamin K approached a normal level of activity and secondary hypoprothrombinemia disappeared.

The influence of streptomycin upon bowel healing at the site of suture in dogs was studied by Poth, McNeill, Manhoff, King, and Sinclair[69]. Streptomycin orally failed to maintain an alteration of the bacterial flora for a sufficient length of time to permit its experimental evaluation in healing of the large bowel. When it was given simultaneously with sulfonamides, the results were essentially those observed when sulfonamides were given alone.

Studies with dihydrostreptomycin have shown that this derivative has no advantage over streptomycin as an intestinal antiseptic, and that it probably favors the development of resistance to a slightly greater extent, as it is less effective than streptomycin against some organisms. Dearing and Heilman[15] have found dihydrostreptomycin to be temporarily effective, but

resistant forms developed after the third day. Bierman and Jawetz[9] claim it has little effect on the fecal flora. In 1950, Riddell[77] carried out a study on patients receiving dihydrostreptomycin specially prepared in tablets for oral use. Total viable bacterial counts, both aerobic and anaerobic, were carried out as well as the coliform counts, and the development of resistance was followed by means of *in vitro* sensitivity tests. Only the coliforms were affected consistently, and even this group built up early resistance to the drug. The other aerobic organisms were irregularly affected, and on the whole it was noted that, as one type of sensitive bacteria was suppressed, another type resistant to dihydrostreptomycin developed and kept the total counts equal to, or higher than, the pre-treatment levels. There was little over-all effect upon the anaerobic counts. On the whole dihydrostreptomycin in tablet form was found to be an unsatisfactory intestinal antiseptic.

During the past few years, attempts[74,75,96] have been made to prevent the rapid development of drug-resistant organisms after oral streptomycin by giving supplemental agents with it, such as aluminum pectinate glucurono-lactone. These materials when given alone by mouth possess no potent *in vivo* antibacterial properties, but become extremely powerful synergistic agents in the gastrointestinal tract when given together with oral streptomycin, far surpassing the ability of streptomycin alone to eliminate intestinal organisms. Wooldridge and Mast[96] showed that the combination of streptomycin and these substances did no more than produce a mild degree of synergism *in vitro*. Mast and Harrison found it possible to sterilize the feces completely in several patients and to eliminate all but a few spore-forming anaerobic organisms in others. This work has been confirmed by Pulaski and his associates[74,75,85], who showed glucurono-lactone to be more effective than the pectin compounds. Most of the patients they studied maintained suppressed coliform counts, with no tendency towards reversion for 14 days. They offered no explanation as to why bacterial suppression was enhanced by these substances. Finegold[28] found streptomycin plus aluminum pectinate much less effective than originally claimed, and both of his 2 subjects receiving this combination exhibited reversion of originally lowered coliform counts within a few days. Donaldson and Bricker[21] found that in 70% of their series of 20 patients receiving streptomycin plus glucurono-lactone, either the coliform organisms or the enteric streptococci developed streptomycin-resistant strains in 48 to 96 hours. There is not enough evidence yet to justify advocating the use of these supplemental agents plus streptomycin to sterilize the colon.

Bacitracin. Johnson, Anker, and Meleney[46] in 1945 described the production and properties of an active principle named bacitracin, obtained from a strain of *Bacillus subtilis*. It is water soluble, very stable below pH 9, non-toxic, and resists digestion with pepsin and trypsin. The bacitracin antibiotic spectrum closely resembles that of penicillin qualitatively, in that it inhibits many aerobic and anaerobic Gram-positive bacteria, but fails to inhibit most Gram-negative species in doses that are clinically practicable. The activity of bacitracin is not impaired in the presence of whole blood, serum, or pus, nor by the presence of large numbers of bacteria. Following oral administration, bacitracin does not appear to be readily absorbed, most of the drug being retained in the feces,

though part may be inactivated or destroyed in the gastrointestinal tract[47]. Bond *et al.*[10] observed great reduction in the number of streptococci and spore-forming anaerobes in the feces of dogs, the count dropping to zero after 4 or more days of oral administration, but there was no effect on the coliform organisms and on cessation of the drug the usual flora returned rapidly. Poth found that low counts can be maintained for at least 2 or 3 weeks on continued treatment, and noted mutual antagonism between bacitracin and the intestinal sulfonamides. Finegold[28] studied the effects of bacitracin followed by streptomycin plus aluminum pectinate in 2 patients, and they showed no better response than patients maintained on bacitracin alone; *Streptococcus faecalis* and the anaerobic spore-formers were reduced in numbers, but the total anaerobes were not affected and there was a prompt rise in the coliform count to high levels. When bacitracin followed streptomycin, the anaerobes were reduced in number to about 1000 per gram of feces before beginning to rise again slowly.

Polymyxin. Polymyxin A (aerosporin or bacillosporin A) was first isolated in England in 1947 by Ainsworth, Brown, and Brownlee[3] from *Bacillus aerosporus*, and at the same time a related antibiotic, now known as polymyxin D, was reported by Stansly, Shepherd, and White[89] in the United States. Later 2 other distinct antibiotics derived from strains of this bacillus were isolated and designated as polymyxin B and polymyxin C. Each of these antibiotics differs from the others in its amino-acid composition. Polymyxin E, isolated in 1949, is identical with polymyxin A in qualitative composition, but speed in partition chemotherapy resembles that of polymyxin B[48]. Polymyxin is highly water soluble, is stable, and its activity is unaffected by prolonged incubation with pepsin, trypsin, pancreatin, and erepsin. Although there have been reports of renal toxicity with polymyxin D, and neurologic and allergic toxicity with polymyxin B and E, the drug is considered to be relatively non-toxic orally, as it is poorly absorbed from the gastrointestinal tract. With a dose of 2 mg. per kilo, body weight polymyxin was not detected in the blood stream or urine[48].

The polymyxins are bactericidal rather than bacteriostatic, and their action is very rapid. One of their remarkable properties is that resistant strains are produced only with great difficulty. They show great specificity for Gram-negative bacteria and are remarkable in being effective against *Pseudomonas;* some types of cocci are affected, but most Gram-positive organisms and *Proteus* are very resistant.

Pulaski, Baker, Rosenberg, and Connell[73] claim that polymyxin is a potent intestinal antiseptic. Solutions of the drug were administered by mouth to 14 subjects in doses of either 200 or 400 mg. per kilo. per day. All Gram-negative organisms except Proteus were suppressed in these 14 subjects within 24 to 72 hours, Gram-positive cocci were reduced inconstantly in number, while clostridia and monilia were unaffected. Suppression of coliforms was maintained for 11 to 24 days, at which times the drug was withdrawn and then coliform organisms returned in from 1 to 6 days. Pulaski, Connell, and Seeley[75] found that polymyxin B rapidly eliminated *Escherichia coli* in 18 cases, and drug resistance did not readily occur; but in 4 cases, *Proteus vulgaris* eventually dominated the fecal flora.

Chloromycetin. Chloromycetin, isolated by Burkholder from *Streptomyces venezuelae*, was prepared as a crystal-

line compound by Ehrlich *et al.*[25] (1947). It is water soluble, stable, and non-toxic. Four isomers have been synthesized in the laboratory, but only one of these possesses the properties of the biosynthesized compound, and this is marketed under the name Chloramphenicol. Its action is bacteriostatic and it is active against *Rickettsia*, some viruses, and some bacteria, including *Salmonella* and the coli-aerogenes group. It seems to be less effective for Gram-positive than for Gram-negative bacteria. Smith *et al.*[87] (1948) showed that chloromycetin is well absorbed from the intestine and that relatively high blood levels occur 30 minutes after oral administration, the drug being quickly detectable in the urine. The small percentage which is excreted in the urine may indicate excessive inactivation by the body, or perhaps excretion by other routes. Hendricks *et al.*[40] mention that chloromycetin can be recovered in the active state from the feces.

Chloromycetin is not generally considered to be a good preoperative intestinal antiseptic. Zenker and Groll[97] report that it effectively reduced the number of bacteria in the colon, and Bierman and Jawetz[9] claim that the normal intestinal flora is significantly suppressed for long periods, allowing resistant "opportunists" such as *Staphylococcus Pseudomonas*, and yeasts to flourish during therapy. Pulaski and his colleagues[74,75,85] do not consider chloromycetin promising, as it suppresses only *Escherichia coli* among the normal intestinal flora. They state that chloromycetin causes *Escherichia coli* to disappear gradually and later become the predominant organism. After initial suppression the total bacterial counts tend to rise above pre-treatment levels and remain high, decreasing only after the drug has been discontinued. Dearing and Heilman[15] gave chloromycetin in doses of 750 mg. 4 times daily for 2½ to 12 days, but did not find it reliable or effective. It therefore does not possess desirable features as a preoperative intestinal antiseptic.

Aureomycin. Aureomycin (also called Duomycin) is a yellow, crystalline antibiotic from *Streptomyces aurefaciens*, which was discovered by Duggar[23] (1948). It is unstable in serum and body fluids, and its toxic reactions have been almost negligible, except for gastrointestinal irritations following oral administration, such as nausea, vomiting, and troublesome loose bowel movements. Nausea and vomiting may be minimized by simultaneous feeding and by giving aluminum hydroxide by mouth. It is prepared as a hydrochloride which is soluble only to the extent of 1% in normal saline solution, but is soluble in water, giving a pH between 4 to 4.5. When made alkaline, it rapidly loses its antibacterial activity. Aureomycin has a wide antibacterial spectrum, including a number of Gram-positive and Gram-negative bacteria, many of them intestinal organisms such as *Escherichia coli*, *Aerobacter aerogenes*, *Streptococcus faecalis*, and *Clostridium*, as well as several of the *Rickettsia*. The action of aureomycin is thought to be bacteriostatic rather than bactericidal. Herrell[42] (1949) recommends it for peritonitis because of its wide range of activity.

Oral administration of aureomycin is preferred, as its acidity in solution may cause irritation at the site of injection. Herrell and Heilman[43] (1949) showed that it is readily absorbed into the general circulation, and is excreted in the bile as well as the urine. Dornbush and his co-workers[55a] have shown that approximately 500 to 600 mcg. are present per gram of wet stool, when 1 gm. of aureomycin is taken orally. Early reports by Finland[29,30] say that as a prophylactic agent aureomycin

has proved superior to the combination of streptomycin and the poorly absorbed sulfonamides. The total bacterial counts of both Gram-positive and Gram-negative organisms in the lower bowel contents drop rapidly and remain persistently low for long periods during oral administration of aureomycin. They noted the appearance of *Proteus* and *Pseudomonas* in the feces of some patients, but from the evidence up to that time, they were not present in large enough numbers to prove troublesome. Pulaski and his co-workers[74,75] have concluded that aureomycin appeared to be of little promise as an intestinal antiseptic, as the coliform count was not reduced to the levels obtained with sulfonamides and streptomycin, and the remaining flora was unaffected. They used a dose of 2 gm. a day. Metzger and Shapse[55] also questioned the value of aureomycin. Following the *Escherichia coli* suppression, they noted an immediate and marked increase in *Proteus* to such a degree that the total Gram-negative count far exceeded the normal count. They state that the development of such a resistant flora may be detrimental.

In studies to compare the effectiveness of aureomycin, sulfasuxidine, sulfathalidine, and dihydrostreptomycin in producing preoperative intestinal antisepsis, Dearing and Heilman[15,16] found aureomycin to be the most effective. They used 750 mg. orally 4 times daily for 3 days, and found elimination of *Escherichia coli, Aerobacter aerogenes, Streptococcus faecalis*, spore-formers, and *Bacteroides*. However, *Proteus, Pseudomonas*, or yeast-like colonies usually appeared in large numbers. Other favorable reports have been given by Fine[27], Zenker and Groll[97], and Bierman and Jawetz[9]. In preparing patients for large bowel surgery, Andina and Allemann[2] begin routinely with aureomycin or similar antibiotic, later adding other chemotherapeutic agents as indicated by sensitivity tests. They have found this procedure of the greatest value in preventing infectious complications in operations on the colon and rectum. Hartl[39] has found that the preoperative use of aureomycin for 3 days in bowel surgery increases the chance of satisfactory healing. Rosenblatt *et al.*[82] suggested that local use of aureomycin in the intestinal tract may be of value when there has not been time for preoperative preparation. Dearing and Heilman[16] caution against using aureomycin in patients with duodenal ulcers, as perforation has occurred after oral aureomycin in a few cases.

Neomycin. Neomycin was isolated in 1949 by Waksman and Lechevalier[93] from *Streptomyces fradiae*. It is water soluble, and non-toxic when given orally, though it causes liquid movements. It is highly resistant to the action of heat and microbial decomposition and possesses strong and rapid bactericidal activity against a wide variety of Gram-positive and Gram-negative organisms. Although it does not favor development of resistant forms, as does closely related streptomycin, it occasionally fails to inhibit the growth of *Aerobacter aerogens*. The optimum daily oral dose for adults was found to be 1 gm. every 4 hours; there is little absorption and no appreciable amount is destroyed by passage through the gastrointestinal tract. Assays of the serum and urine would indicate that what is absorbed from the gastrointestinal tract is rapidly excreted (about 3%) by the kidneys. The major portion of the antibiotic is passed in the feces unaltered, and will be found in the stools in a concentration of approximately 10,000 gamma per gram of wet stool.

Poth and his co-workers[65,66] gave neomycin with sulfathalidine to prevent

the development of the occasional resistant strain of *Aerobacter aerogenes*, and ordinarily the total intestinal flora is reduced to less than 100 organisms per gram within 24 to 48 hours after the first dose of the combined therapeutic agents, provided castor oil is given initially to evacuate the bowel completely. Shortly after the bacterial flora has been reduced to extremely low numbers, yeasts become abundant. Neomycin exerts a profound effect on the bacterial flora of the bowel for 24 to 36 hours after administration of the last dose of the drug. After the bacterial flora has been altered by oral neomycin, it is claimed 0.1 gm. of patient's feces per 20 gm. of mouse produces no ill effect.

Pulaski[72] considers neomycin, 4 to 6 gm. daily for 3 days, to be a reliable intestinal antiseptic when used in conjunction with low-residue diet and an enema. Dearing and Heilman[16] showed that in general the number of organisms was greatly reduced when the patients were prepared with neomycin; and cultures gave no growth of *Escherichia coli*, *Aerobacter aerogenes*, *Streptococcus faecalis*, *Proteus*, *and Pseudomonas*, but *Clostridium*, *Bacteroides*, and green-producing streptococci were frequently present.

There has been no evidence that the bleeding, clotting, or prothrombin times have been prolonged in the slightest, even with as long as 6 weeks of continued therapy.

Terramycin. Terramycin was described by Finlay *et al.*[31] (1950) and is derived from *Streptomyces rimosus*. It is a highly stable crystalline amphoteric substance of low toxicity, but may cause intestinal irritation, nausea, and vomiting. Crystalline terramycin is soluble in water only to the extent of 0.25 mg. per cc. at 25°C. *In vitro* and *in vivo* studies indicate that terramycin has a wide bacterial spectrum. It is effective against many aerobic and anaerobic Gram-positive and Gram-negative bacteria, including the Gram-negative enteric organisms, aerobic spore-formers, and Gram-positive cocci. *Pseudomonas* and *Proteus* in the main are moderately resistant to its action. Terramycin is bacteriostatic in threshold concentration, and bactericidal in high concentration. It is readily absorbed from the gastrointestinal tract, producing significant blood concentrations, and is excreted in the urine in a biologically active form, though large amounts are inactivated in the body. Herrell *et al.*[44,45] have shown that a great deal of terramycin administered by the oral route is not absorbed but is excreted in the feces. It was not uncommon to find as much at 2.5 mg. of terramycin per cc. of feces in patients who were receiving multiple doses of the antibiotic, and Welch[95] reports that large amounts of terramycin were found per gram of the contents of the large intestine. After an optimum point of absorption is reached, an increase in the dose of terramycin will increase the amount excreted in the feces. Hendricks *et al.*[40] also comment on finding terramycin in the feces, but they note that with this drug, as well as with aureomycin and chloromycetin, a higher percentage of the drug ingested can be recovered from the feces after low oral doses (0.5 gm.) than after higher doses (1 to 2 gm.).

Studies in a few cases[44,45] demonstrated that the feces became odorless and the clostridia, streptococci, and coliform bacteria disappear; the only remaining forms being yeasts, *Candida*, and micrococci. DiCaprio and Rantz[18] consider their 7 patients show that terramycin had a pronounced effect, which was evident after 36 to 48 hours, on an oral dosage of 3 gm. daily. The ordinary aerobic bacteria of the bowel were reduced to less than 2000 organ-

isms per cc. of wet stool, but in several cases resistant strains appeared after a variable number of days, some of which had not been found previously; others had been observed to be sensitive earlier. Baker and Pulaski[6] found in 11 patients that oral terramycin eliminated coliform bacteria from the feces, while Gram-positive cocci were inconstantly suppressed and *Proteus* dominated the flora as other organisms disappeared. With a priming dose of 2 gm., followed by 0.5 gm. every 6 hours for 5 days maximal suppression occurs in about 72 hours, showing 400 to 1600 mcg. of terramycin per gram of wet stool. On withdrawal of the drug, *Escherichia coli* and fecal streptococci returned to normal strength, while *Proteus* continued to be present. Rivera and Sborov[78], giving 4 gm. of terramycin daily, obtained complete suppression of certain bacteria, starting 48 hours after initiation of therapy and continuing for as long as 38 days. Two grams daily lowered counts irregularly, with a return of bacteria after a varying period of time to pre-treatment levels, despite uninterrupted administration of the antibiotic. *Candida*, *Proteus*, and *Pseudomonas* grew better and multiplied more rapidly in an environment in which other enteric organisms had been largely suppressed. Dearing and Needham[17] recommend a dosage of 750 mg. orally 4 times a day for 3 to 3½ days. They found that all culturable microorganisms failed to grow except *Proteus* and *Pseudomonas*, certain coagulase-negative micrococci, and occasional strains of *Aerobacter aerogenes* and *Streptococcus faecalis*. Yeasts tended to increase in numbers.

Inference. The ideal drug or combination of drugs for intestinal antisepsis has yet to be found. The surgeon desires strict avoidance of contamination with fecal bacteria, and so the search still goes on, despite the possibility that sterilization of the bowel may be unnecessary, or a disadvantage, or impossible. The impression is gained that existing measures allow the suppression of certain species and multiplication of others, without reducing the total numbers of bacteria in the feces and with the added menace of replacement with resistant strains. Poth[66] outlined the properties of the ideal intestinal antiseptic as follows: 1) Low toxicity for the patient; 2) broad bacterial spectrum; 3) prevention of development or overgrowth of resistant bacterial variants; 4) rapid activity; 5) limited absorption from the gastroenteric tract; 6) permits adequate food and fluid intake; 7) assistance in mechanical cleaning of the bowel without causing dehydration; 8) will not cause gastroenteritis; 9) promotion of tissue healing; 10) low dosage; 11) soluble in water; 12) palatable.

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PREVENTIVE MEDICINE AND EPIDEMIOLOGY

UNDER THE CHARGE OF

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THE BIOLOGICAL AND SOCIAL SCIENCES IN AN EPIDEMIOLOGY OF MENTAL DISORDER

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MEDICINE has 3 general methods by which to develop knowledge of disease. No single one suffices to the exclusion of the others; each has its individual usefulness, and the fullest measure of progress is to be expected when all are brought into action. The 3 methods are the clinical study of the individual patient, laboratory experiment, and the epidemiological approach through field and statistical study of disease as a mass phenomenon of groups of people. The potential capacity of each method to contribute to a common knowledge becomes evident where the aim is research. The principle holds equally in examination of a particular disease situation, when the knowledge gained is to be turned to practical management, control or prevention. The relative usefulness varies from disease to disease, and according to the specific objective. Epidemiological analysis is not to be construed as a substitute for either of the other methods of study, but as an addition.

The present purpose is to examine the extent to which epidemiological methods may be applied to mental diseases and emotional disturbances. A further aim is to see how existing techniques for mass measurement of disease may be adapted and enlarged to meet the needs of this field, specifically through correlation of the biological and social sciences. The final effort is to judge the likelihood and presumed direction of practical additions to prevention and control, evolving through epidemiological means.

EPIDEMIOLOGICAL ACTIVITIES IN MENTAL DISORDERS. Viewed in relation to the whole of medical effort, mental disorder is no facile field. Clinical identification of individual illnesses is frequently none too certain, classification of disease is indefinite, and studies on the physiology and biochemistry of the brain and of the endocrine organs have scarcely kept pace with those in some other parts of medicine. The principal justification for epidemiological methods in this area is that the total situa-

tion is such as to warrant bringing the whole of medical firepower to bear.

When epidemiology escaped its restriction to the communicable diseases and began to explore other mass disease as reflected in degenerative[19] and neoplastic processes[69], and in physical injury[38b], the field of mental illness was attractive.

Statistical data on emotional and other mental disorder had been collected for many years, principally in relation to hospital patients and to deaths, and primarily for administrative purposes. Much order was introduced in this effort by the adoption of the first formal classification of mental diseases in 1916. Elkind[28a] was one of the first to suggest that the data could be used for epidemiological purposes[28b], although he gives the original credit to Rosenau. At the First International Congress on Mental Hygiene in 1930, Emerson[29a] gave quantitative evidence of the magnitude of nervous and mental diseases as a public health problem, and some years later outlined an epidemiological approach[29b] to diseases of this class. It is not surprising that Freeman[35] who was first in so many fields of epidemiology, provided the stimulus for a comprehensive field survey of mental illness in a general population[13a,b,14,15], in the Eastern Health District of Baltimore. As mental illness was progressively incorporated into modern public health activities[110] and trained public health workers[93] were attracted to the field, epidemiological studies[66a] were a natural precursor to organization of formal programs[65b]. New York[77b] and Massachusetts[20b] took the lead among official state agencies, with Treadway[128] active in the national Public Health Service.

World War II gave a decided impetus to the group approach to mental disorders, because of problems of the armed forces. Preventive psychiatry[4a] was developed through an epidemiologic approach, to such an extent that the association of mental health and epidemiology came to be accepted procedure in operational activities in the field[38a], in the management of recruits[43], and at administrative levels[5].

The stimulus originating in war activities gained ground in the years that followed, through detailed presentations of mental illness as a part of public health[65a], both in this country[34] and in Britain[45b]. The Milbank Annual Conference[30] of 1950 did much to crystallize thought in epidemiological developments. Increasing attention is given to technical method[17]; and long-term field studies are underway in at least four centers in the United States[99].

Psychiatrists progressively appreciate that epidemiology is something more than detective work designed to track down a causal agent with the purpose of applying preventive measures against its action. Epidemiologists, through association with social scientists, psychologists, anthropologists and psychiatrists, are gaining a better understanding of group characteristics of mental diseases, and also an insight into potential application of the social sciences to other kinds of mass disease.

A frequent interpretation of the difference between a clinical and an epidemiological approach to disease is that one method of study is intensive, the other extensive; that one deals with small groups, the other with large; and often the implication follows that small groups are always well-studied and large ones have inescapable errors. The clinician usually deals with small numbers, but given modern field and statistical techniques that is also within the province of the epidemiologist. The principle in both instances is the existing difference between control and observed values. If the difference is great,

small numbers suffice; if it is small, numbers must be greater. The variation in worth of basic data inherent in large numbers of cases because of contributions from many workers can be tested statistically for reliability and extent of error. Even rather faulty material sometimes yields data of real importance.

The fundamental difference in the two methods is that mass phenomena of disease do not represent a summation of the effect evidenced by the individuals that make up that group; but rather that communities, through interaction of the persons included, have physical and mental characters as well set apart as those of a single individual. A second consideration is the unit of observation which in clinical medicine is the sick individual, while in epidemiology it is the composite of sick and well that constitutes a community. The results to be derived from the two methods of study are sometimes strikingly individual, with one providing contributions not possible with the other.

Epidemiology as Medical Ecology. Many kinds of evidence from the field, from clinical studies and from accumulated laboratory investigations contribute to an interpretation of epidemiology as medical ecology[38c], wherein disease and health are seen as no more than selected instances among the many results of the total interaction between man and his environment. Ecology[1] is a biologic and social discipline concerned with the general phenomena of mutual relationships between living organisms and their reaction to animate and inanimate surroundings. That part of human ecology relating to health and disease is medical ecology, and medical ecology as it concerns communities of people is epidemiology.

With disease and injury regarded as problems of ecology, their behavior qualitatively and quantitatively is a matter dependent on the kind of balance, the nature of the biologic equilibrium currently existing between a living organism and its environment. In every sense this is a state of balance that varies from time to time and under a variety of circumstances.

Medical ecology attempts to develop a pattern into which may be fitted the separate sciences relating to the health of man. Its function is to unify numerous and divergent disciplines often differing greatly in primary interests; and to bring each into an ordered place in a generalized study of human disease. Disease is interpreted as a maladjustment between a host and the existing environment. The study of mass disease of human populations thus entails the necessity to deal with the community as a unit, a complete whole, all things living and non-living within a prescribed universe, if the particular concern of man himself is to be adequately understood. This is the precise business of epidemiology.

Modern medical attitude in classification of disease is etiological, in terms of the agent directly concerned in causation. Where agents such as a microbe, alcohol or lead have been demonstrated, consistency is maintained by separating the agent from environment and recognizing it as an element. The pattern of ecologic analysis then consists of a triad, the members of which are the human host, an agent of disease, and lastly the intricate complex of environment. Lacking demonstration of an agent, the simpler formula holds. Opportunity will be had to enlarge on the individual part that host, agent and environment have in the larger scheme of mass disease and to illustrate by specific situation that causation is regularly a product of all three, but that frequently one factor or another dominates a particular situation.

MULTIPLE CAUSATION OF MASS DISEASE. A concept of mass disease in terms of ecology leads directly to an interpretation of cause as multifactorial. Present day epidemiology stresses the importance of the agent of disease largely by reason of the better methods and the greater ease with which this factor is measured and appraised. The concept of multiple causation does not discount the specificity of disease where agents are known to exist, but recognizes the agent as no more than one of the causes, important as it is. The principle evolves that causation of mass disease resides in a combination of variables, variously derived from two broad sources, a host population attacked and the environment in which that host lives.

CAUSAL SYSTEMS. Two causal systems are to be distinguished. The first includes a series of interrelated variables of which one, commonly an agent of disease, is a necessary requirement. Subdivisions are recognized in situations characterized by the presence of an agent, as in lead poisoning, and in general paresis among mental diseases; in those marked by absence or deficiency of an agent as a particular vitamin in ariboflavinosis; and conceivably, a third subdivision where an agent exists but is unknown.

The second system represents an association of events or factors in such combination and at such time that disease results, but with no single constituent invariably essential and active. Varying combinations of factors may produce the process. Examples are cirrhosis of the liver, appendicitis and cardiac decompensation. Presumably many mental disorders are of this category.

Variability of Cause. To assume that the combination of factors responsible for a particular disease situation in a community is fixed and constant, is a deterrent to proper interpretation of disease mechanisms and disease behavior. The belief nevertheless exists, whether the causal system is of the first or second order just noted. What holds as the totality of cause today is not necessarily characteristic of tomorrow, nor does it assuredly coincide with yesterday. The ecologic relationships of the community host are altered continuously and thereby the constituents of the causal complex. Epidemic malaria has been cited in illustration[132]. That similar diseases and similar epidemics may arise from dissimilar causes is established principle. This requires that all factors entering into disease production and disease distributions be kept in view at the same time and each in relation to the other.

Theory of Causal Action. A frankly deterministic interpretation of one element acting directly on a second, the host, is outside a concept of multiple causation, even in such simpler situations as a Cocoanut Grove disaster[12]. Considering the mass phenomenon, a variety of environmental and host factors determined the ultimate result of the numbers injured or dying of burns.

Action through a concatenation of factors, where a series of things depends one upon the other as if linked together in a chain, seems scarcely a universal explanation of the genesis or limitation of mass disease. The traditional chain of infection, where an agent passes out of one host and into another, is reasonable enough with many communicable diseases. Success in control comes through interruption of the infectious agent at any specified point in the circuit, and yet controlling water supplies does not alone put an end to typhoid fever. For most mass diseases of non-infective nature and for mass injuries, the hypothesis scarcely seems tenable.

That mass disease in general is the resultant of forces arising from a variety of sources and each interacting with the others, that it follows physical laws where positive or disease producing values outweigh the negative or protective forces, is suggested as a working hypothesis. The result is a disturbed equilibrium marking a departure from the norm that is health. The direction of effect and the extent of reaction presumably are determined by the dominant components of a complex causal system. The explanation of mass disease is presumably not to be found in isolated factors, nor in series of factors each operating independently, but rather in a combination of mutually interacting variables that together form a causal system. The hypothesis is suggestively pertinent to mental disorders.

Practical Approach. Accepting as valid the concept of multiple causation and the stated hypothesis of its mechanism, the practical approach in investigation of cause is first one of analysis and then of synthesis. Single factors in causality are to be identified and weighed in terms of their independent effect, through measuring incidence and recording the character of movement of a disease through a population. Using statistical techniques of single variable analysis, studies have been made of biological[23] and sociological[86] variables in many diseases, including mental illnesses[20a]. The critical need and the anticipated second step is to determine the interaction of multiple factors each upon the other, through multivariable statistical procedures. These methods have had much use in communicable disease[53b] and are not unknown in the area of mental disorders, Hammond[46] having studied 4 variables, sex, age and two associations of sociological variables in relation to first admissions to mental hospitals.

Prevalence and Incidence of Mental Disease. A first step in the study of any general field of mass disease is to determine the broad nature and extent of the problem. Deaths provide the readiest index, because they are a matter of official record. A satisfactory knowledge of case fatality gives a working approximation of incidence of cases. With additional knowledge of average duration of illness, a fair idea of prevalence is possible. Tuberculosis provides an illustration.

Although some diseases are a chief cause of morbidity, of themselves they cause practically no deaths. Mental illness is of this order[65b], with general paresis one of the few directly responsible for death. An opinion on frequency of occurrence depends in such instances on knowing the numbers of cases. The information may be had from official reports, or alternatively, through a direct census of cases. Because of practical limitations, this is usually accomplished through an adequate sample that permits generalization.

Knowledge of occurrence requires 2 kinds of information. The first is the number of persons in a community affected at any given time, which is prevalence; and second, the rate of occurrence of new cases within prescribed units of time, which is incidence. From rates of incidence in sufficient series, trends can be determined. With these rates, crucial answers are to be had of the absolute size of the problem, the relative size in respect to other known classes of mass disease, and whether the problem is decreasing or increasing. Specific questions of causes of origin or how the situation developed are not involved.

To know the extent of a mass disease permits 2 lines of action. The first

is operational, with measures of prevention and control directed towards those diseases or subclasses where adequate knowledge exists. Preliminary recognition and separation of such divisions necessarily enters into the total count. Direct administrative action is possible for few mental illnesses because of technical difficulties and because of limitations in what is known of their mass behavior. The second line of action is research and investigation of causes of origin and course in respect to individual disease entities demonstrated significantly important.

The stated pattern of procedure in determining incidence and prevalence of general mental disorder is theoretically simple but administratively difficult, because mental diseases are not reportable. The procedure is technically inexact because of existing limitations in knowledge of the diseases themselves along with lack of satisfactory methods for mass case finding. Summed up, the obstacle lies in what to count, what is mental illness.

When an outstanding psychiatrist[59] views information from one of the oldest and best recognized sources as suffering from "the low level of psychiatric knowledge on which these records were based, and on the notably poor records which exist even now in many state hospitals, the disagreements regarding diagnosis among various psychiatrists, the conflicts in conceptions of what various diagnostic terms mean, in fact the unholy mess of nomenclature" and then states a preference to "write a paragraph of description and psychodynamics than to use one single diagnostic term," the epidemiologist is likely to hold his head in his hands.

The difficulties in definition and classification are admittedly many and deep-seated. Diagnostic terms now used do not include all conditions considered by many as among mental health problems. A tendency exists to think of mental disturbances essentially in terms of chronic illness. Many have acute and reversible phases to confuse interpretation, but so does undulant fever. The ordinary conceptual scheme of disease may not be applicable to mental disorder but there must be some basis for decision between normal and abnormal, and for identifying that abnormality. Serious attention is being given these matters of nosology by a committee of the American Psychiatric Association[2].

Eaton[27] has stressed the futility of trying to define mental health by any one standard and lists as 5 possible criteria, clinical insight, conformity to an ideal personality description, self-appraisal, a group judgment and a statistical norm. A decision based on any one is suggested as open to criticism.

Lacking clear definition of mental health, it follows that mental disease likewise remains equivocable. Until clinical methods provide a valid basis for classification, epidemiology can scarcely give proper information or variations in distribution of a disease, nor compare frequencies in different areas, nor in relation to other similar disorders; hence the earlier emphasis on intensive clinical research.

Another approach to better basic data is through laboratory experiment to provide technical means for precise recognition of a disease. When methods became available to distinguish patients with epilepsy from other persons through cerebral dysrhythmia in the brain wave pattern[68], the way was clear to investigate host and environmental factors tending to precipitate seizures[11].

Lacking progress in either of these directions, application of epidemiologic method is possible through adopting an arbitrary or operational definition of a condition in the way that Hooton[52]

did when he recognized as criminals those who had been in prison for a felony. Important limitations are necessarily accepted, first that the definition sometimes eliminates a characteristic one wishes to measure; second, that a specific characteristic is so restricted that measurement is purposeless; and third that the results obtained apply only to the selected population, not universally.

Existing information on prevalence and incidence of mental disease has been drawn from 4 main sources, to the greatest extent from patients in mental institutions, from data incident to operation of selective service systems for military duty, from experience with military populations in time of war, and from field surveys of general populations.

Prevalence. The main studies on prevalence as determined by patients in mental institutions, are from records of New York[77b] and Massachusetts[20b]. The findings have been critically reviewed by Gruenberg[30]. They give a rough estimate of prevalence rates for severe mental diseases and some indication of those segments of the population most affected. The main limitation[66f] is the lack of a base by which to relate these facts to a general population. It is essential to avoid the tacit assumption that committed cases consitute a random sample of a population and that the population itself is indeed normal.

The only practical way yet discovered to approach the problem of prevalence and incidence of mental disorder in large geographical or political units[66f] is to gather information through population samples. The Eastern health district survey in Baltimore[66a,b,c,e] drew on records of 43 public and private agencies, including police, social service, and hospitals. Severe illnesses requiring admission to a mental hospital naturally were counted, but the bulk of information related to more ordinary situations within 10 categories that ranged from "psychosis" to "adult delinquency without other information." The result was a prevalence rate for active cases occurring during 1936. The study is one of the better sources of information. The high quality of the social and medical services in the area made this review of records a satisfactory substitute for the preferred procedure, which is direct field survey of a population.

An actual house to house count of mental disease was made in Williamson County, Tennessee, where some 15% of a rural population of 24,804 was sampled by repeated visits. This was a part of a larger study of the total population where information was had through referrals by nurses, physicians, teachers and others in key positions. The criteria for mental disorder were "cases that could be referred to a mental hygiene clinic." Data from the more extensive referral study have been used to determine a 1-day prevalence[110] of active and inactive cases of mental disorder as of September 1, 1938.

Incidence. A recurring theme of the past century has been the steadily rising incidence of mental disorder in most civilized countries. The usual basis of judgment is numbers of first admissions of patients to mental hospitals, as in Fig. 1. Numbers and rates certainly have increased but the data do not measure mental disease in a general population[66f]. The increasing number of beds available for mental patients naturally leads to greater rates. An aging population has the same effect. Committed cases dominate the older groups (Table 1) and the more older people the greater the total rates, even with age specific rates

remaining unchanged. Urbanization also tends towards increased rates, as judged by comparative observations for New York City and upstate New York[77b]. On the basis of first admissions to mental hospitals in Massachusetts, New York and Illinois for the periods 1919 to 1921 and 1929 to 1931, Dorn[22] concludes there is no alarming increase. Despite a 15% overall accretion in this 10-year period, rates for both sexes below age 40 years were actually lower[80a].

Exact data on incidence of mental disorder in general populations, to be had through field survey, are almost wholly non-existent, to a greater extent even than for prevalence. In a thorough analysis of such as are at hand, Lemkau *et al.*[66f] find a common inadequacy of method and a complete inability to make reasonable comparisons because of changing criteria in the course of time-trends.

Newly initiated studies[129] in Massachusetts make use of another approach toward the desired information. A prevalence value of general mental disorder is sought by determining all persons receiving psychiatric care during a given month, to include facilities provided by hospitals, by mental hygiene clinics, and through private practitioners. Such information permits study of the individual characteristics of the group, and the determination of variables distinguishing these persons from others of the community. This epidemiological procedure is much used in other mass disease and conceivably is applicable to mass mental disorder.

In illnesses where a reversible phase or low-grade chronicity is as frequent as in mental disorder, a follow-up of patients discharged from mental hospitals would seem useful. Those with apparent arrest would be separated

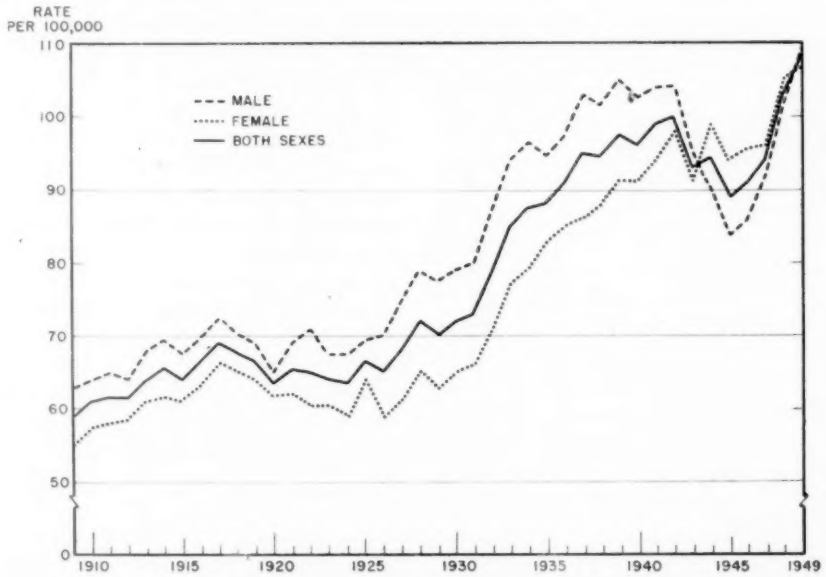

FIG. 1.—Mental Disorder: First Admissions to the New York Civil State Hospitals, Per 100,000 Population, 1909-1949. Source: Data from Annual Report, 1949, of the New York State Department of Mental Hygiene.

from those under continued observation in mental health clinics or by private practitioners. Such studies would presumably contribute to improved interpretation of prevalence, to measurement of efficiency in control and management, and most usefully in a better understanding of cause and course through search for characteristics in which those who recover differ from those who do not.

TABLE 1.—AVERAGE ANNUAL RATES OF FIRST ADMISSIONS TO MENTAL HOSPITALS PER 100,000 POPULATION FOR AGE AND SEX IN NEW YORK STATE, FISCAL YEARS 1939–41

Age (years)	*Males*	*Females*	*Total*
Under 5	0.54	0.41	0.48
5–9	7.17	2.51	4.89
10–14	10.77	6.60	8.71
15–19	60.06	50.51	55.29
20–24	103.96	80.56	91.83
25–29	111.22	102.91	106.85
30–34	124.89	110.69	117.58
35–39	134.20	121.01	127.56
40–44	140.31	116.06	128.28
45–49	144.67	132.86	138.89
50–54	164.58	145.39	155.33
55–59	172.61	149.32	161.21
60–64	213.46	179.66	196.35
65–69	282.50	240.27	260.35
70–74	375.02	319.00	344.97
75 and over	679.26	603.30	636.44
Total	121.90	109.22	115.51

Source: Malzberg, B.: Psychiatric Quart., April, 1949, p. 6.

For the selected age group that characterizes a military population and under the atypical conditions that govern in war, rather useful information[4b] in respect to prevalence of mental disorder came to hand in recent years, principally because of the good reporting system under military conditions. The difficulties already stated came into play in attempting comparison with experience in the preceding war[5] of 1918, in comparing experience in different theatres of operation, and in attempted definition of time trends. The chief gain was epidemiological understanding[4a] of such factors as length of service, battle experience, quality of leadership and similar factors[48a,b] in determining frequency of emotional disturbance. Selective service examinations[111,112] on the scale of recent experience were of such magnitude as to tend to even out local variations in interpretation and schemes of classification, permitting a fairly good idea of what the medical profession believes to be the frequency of the more important mental disorders[95] in the age group concerned. Segments of experience gave particular information on determining factors, for instance frequency by residence[43].

The class of morbid processes distinguished as mental illness is an artificial grouping of many conditions having a varying emotional component. The quantitative interpretations just presented depended upon recognition of disease entities or clinical groupings, presumably representing together the total field. They were then combined. Suggestions as to causes of origin and the nature of distributions in population groups were a frequent by-product, although the purpose was no more than to define the limits of the field. What has been outlined thus far is an elementary epidemiology.

Epidemiological Analysis of a Single Disorder. The more serious effort of identifying origin of mass phenomena, of determining distributions in fractions of populations, and the movements in time and place is through study of disease entities, either clinically or etiologically determined. The questions stated are of specific nature. They require study on a controlled basis. Mental disorders with some physical component and possessing features common to other mass diseases already defined in their group relationships, are seemingly best

suited to such studies. Drug addiction, drug habituation, alcoholism, multiple sclerosis, general paresis, pellagra and suicide are possibilities.

To attempt epidemiological analysis of all mental disease as a unit is to invite difficulty and confusion; to undertake study of intricate processes and less well-defined diseases without a basic method and a pattern of study developed through more favorable material, is not good sense. When the relatively simple is understood, the more complex can be undertaken with discrimination and an ability to devise crucial experiments. Several considerations have influenced the present selection of suicide as the condition around which to develop a content of epidemiologic analysis in mental disorder.

Suicide is a fact, under most conditions easily recognized and correctly recorded. The contributing factors are subject to differences of interpretation, but rarely the primary cause of death.

A mental component of suicide is recognized. Of 3631 deaths from suicide in the United States[62] in 1940 with secondary cause recorded, mental disease and deficiency was noted most frequently, in 1411 (39%). Lewis[7] states that those who commit suicide or make serious attempts are in a pathologic mental state of the dimension of a psychosis, which cannot be assumed absent despite previous lack of symptoms.

Suicide is an important public health problem long recognized as such[25]. The 16,354 deaths of 1948 rank suicide eleventh among leading causes of death in the United States, far exceeding such communicable diseases as poliomyelitis with 1895 deaths and whooping cough with 1146.

Suicide is the one situation among mental disorders where analysis of the mass problem can be based on deaths. The data have a reliability comparable with those of tuberculosis.

The data are believed relatively inclusive. The International List of Causes of Death[79] includes as suicide, self-inflicted death by poisons including gases, hanging, drowning, fire arms, cutting or piercing instruments, jumping from heights, and others. Some forms of self destruction are less exact, for example, suicide by means of automobiles is for the most part recorded as accidental death. Not all self-inflicted death by poison is listed as suicide, for example, ethyl alcohol[83c]. The social stigma attached to suicide will cause some false recording. The opposite error of including non-suicide deaths is presumably rare.

Biologic Gradient of Suicide. The totality of a disease process extends from minimal departures from an established norm, termed health, to severe manifestations commonly resulting in death. This has been termed the biologic gradient of disease[38c]. Death may occur at any point in the gradient, although naturally it is clustered at the extreme of more severe pathological change. Lindemann[73] has developed a conceptual scheme of a biologic gradient of suicide, seeking to establish a specific relationship between a common underlying conflictual pattern and the more specific end point of suicide. The range is from aggression through psychosis to depression. The clinical result is variously expressed as consideration of suicide, attempted suicide or death from suicide. This scheme requires a definition of psychiatric conditions far less definite than suicide itself. The same lack of preciseness in identification and definition of minor manifestations often holds for other morbid processes, for example, diphtheria.

No adequate data exist on the proportion of a population who have

considered suicide, but not actually attempted it. Eighty percent of 200 university students in sociology[8] gave a positive answer when asked that question. Oliven[92] questioned 50 apparently healthy normal people about suicidal thoughts and impulses. Seven could not remember having ever thought of it, to 4 the idea was abhorent, and 39 admitted such thoughts. This meager information suggests an appreciable prevalence of suicidal ideas.

Studies of hospital patients[83a] suggest that attempted suicide[122] is not a characteristic of the same population groups that actually commit suicide. For example, more women than men[67] and younger rather than older persons[97] attempt suicide, which is the reverse of age and sex distributions in successful suicide (Table 2). Absence of an accepted classification of attempted suicide precludes comparison of hospital data and clearly eliminates relating the information to a general population. As Raines and Thompson[101] point out, genuine attempts and false gestures are distinctive in their underlying psychopathology, but are often similar in outward manifestation. A person may make a suicidal gesture to attract attention, with self destruction the last thought in his mind, and yet the attempt may bear all the earmarks of a genuine suicidal attempt. Another person may be clumsy in an actual attempt, but as a result is thought to have made a gesture.

The present analysis of fatal cases admittedly deals with a small segment of a total morbid state, but is so chosen because usable data are to be had in this particular area. A study restricted to fatal cases has the same limitations that apply to poliomyelitis or any disease of man, aside from exceptions such as rabies. To an extent, satisfactory information is to be had of mass relationships as the disease attacks a total population. Understanding of the total process of poliomyelitis, and likewise of suicide, requires an expression in terms of morbidity, and morbidity is based on an understanding of the various biological gradations which constitute the total process.

Movement of Suicide in Time. Good records of suicide are available for France since 1817, and with some limitations for Germany[84] for much the same period. Data from England and Wales[126] and for the United States (Fig. 2) cover a shorter interval. All give proof that suicide does not occur at a regular rate.

Through simple relation to events of the times, the general pattern in all countries suggests that suicide is less frequent during wars and more frequent during economic depressions. The causes of course are not in those events themselves but in the effect they have on the host population or the environment of that host. That brings need to examine these constituents, to search additionally for explanations of why suicide is more prevalent in some countries than in others, and to view the fundamental question of what induces man to self-destruction. The elements of host, agent and environment are examined in turn with the purpose of identifying particular factors in causation of suicide, with no suggestion that they act individually or that cause is anything else than the resultant force derived from multiple contributions originating in all 3 sources. Material differences in combinations of causal factors are expected and recognized in different cultures and under varying circumstances. Suicide is a clinical entity, death by self-destruction, but not a specific disease.

HOST FACTOR. Interpretation of what constitutes host factor in disease causation is often flavored by the nature of the condition under study and by the interests of the investigator viewing the problem. Thus host factor in communicable disease is likely to be considered essentially an acquired characteristic resident in definable antibodies; in neoplastic disease as largely a matter of genetic inheritance. In chronic degenerative diseases the direction of interest is toward changes in anatomical structure and physiological state associated with growth, development and aging of the human organism.

Analysis of host factor in any mass disease, in this instance mental and emotional disorders, is aided by a framework within which to fit the constituent parts. Some host characteristics are innate and some are acquired, some are permanent and some temporary. They are here distributed within 5 general categories. The relative contribution to causation expectedly varies from one mass disease to another, but commonly all are represented. The illustrations are primarily from suicide.

Intrinsic Factors. The simple characters of the human host that reside in age, sex and race are among the more significant determinants of mass distributions of disease. They act through physical alteration of anatomic structure and physiologic state, and also as social factors.

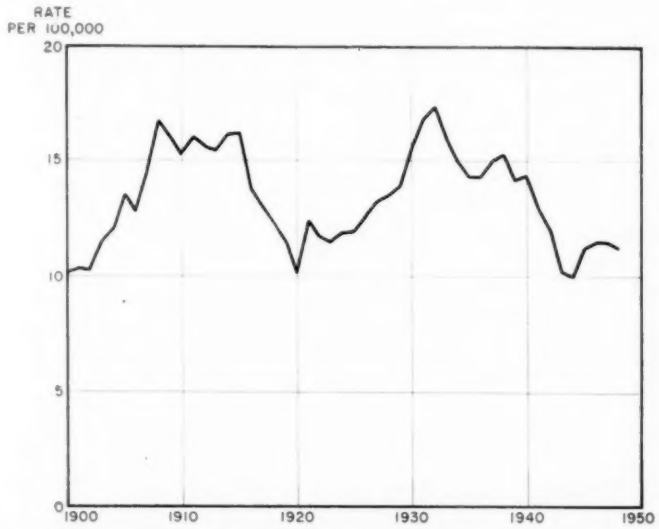

FIG. 2.—Suicide Rates Per 100,000 Population, Death-Registration States, United States, 1900-1948. Source: Vital Statistics of the United States, 1948, (National Office of Vital Statistics, Federal Security Agency, United States Public Health Service).

Age. That suicide "augments in direct ratio to age" is as true today as when Morselli[84] first presented evidence of that fact 70 years ago. Furthermore it holds for all countries where such studies have been made[56]. The data for the United States are in Table 2. Distinctive age distributions are a feature of mental diseases such as schizophrenia and senile or arteriosclerotic psychosis. This is in contrast

to manic depressive psychosis, general paresis, alcoholic psychosis, and involutionary melancholia which occur at much the same ages, suggesting a common basis effected by different precipitating mechanisms[63].

Sex. Male rates in suicide rise steadily from age 15 years, while those for females level off after the fifth decade. In Western Europe and in the United States the relation of male to female suicides has continued for

TABLE 2.—SUICIDE BY AGE AND SEX PER 100,000 WHITE POPULATION, UNITED STATES, 1940

Age	*Male*	*Female*
0–9	—	—
10–19	2.5	1.6
20–29	15.8	6.3
30–39	25.0	10.2
40–49	36.3	13.1
50–59	52.2	13.5
60–69	59.0	13.3
70+	62.3	10.2

Source: Vital Statistics of the United States, 1940 (Bureau of the Census).

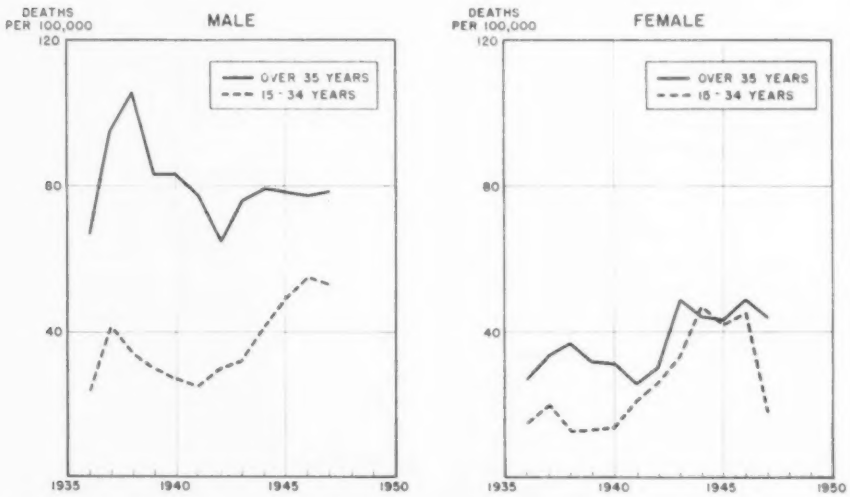

FIG. 3.—Male and Female Suicide Rates Per 100,000 Population, by Age, Copenhagen, 1936-1947. Source: Annual Reports, Health Department of Copenhagen, Denmark.

many years in the proportion of about 3 to 1. The decreased total rates in time of war are more a function of the male rate than that for females (Fig. 3). In certain countries where the impress of wartime conditions was pronounced, rates for females actually increased[3]. The fundamental sources of these differences in sex distribution are to be sought through analyses of occupation, of various cultures, and of physiological state, as Jellinek[54] has done for alcoholism.

Race. Appreciable differences in suicide rates have been a consistent feature of the various racial fractions of the United States population. In 1940 the suicide rate for Negroes was 4.1 for 100,000 compared with a white rate of 15.5; that for Chinese was 45 and for Japanese 26 per 100,000. Explanation on a purely racial basis is insufficient. A study of attempted suicides in Cincinnati[97] demonstrated that the Negro rate is strikingly higher than expected, suggesting cultural

variations in northern and southern Negro populations. Faris and Dunham[31] have shown a similar effect from social environment in other mental disease. A changing social order has often eliminated presumed racial differences in rate of attack for such conditions as pellagra[40] and has had a demonstrable effect on the relative frequency of syphilis in Negro and white populations.

Psychical Constitution of Populations. Community health surveys to determine the general physical state of a population have been an epidemiological development of recent years. Sometimes an active census[96] of disease and injury was taken at a prescribed time. The community survey of Roth and Luton[110] is a specialized counterpart in respect to mental state. Correlation of levels of total mental illness with suicide rates and search for a specific element among minor mental disorders, psychological abnormalities and major commitable disease unduly associated with that condition are possible uses of such material. Salmon[113] for instance states that one-third of suicides have frankly commitable mental disease, of which 70% are manic depressive psychotics.

Under other circumstances the state of physical health of a community has been determined indirectly through consideration of the nutritional qualities of the community population. The principle has been little employed for mental disorder. The necessary practical field methods are yet to be developed. Presumably they lie in the work of Pavlov[94], Cannon[7], or in the newer developments associated with ACTH whereby emotional feelings and attitudes are determined on a physiological basis. An alternative is in psychological tests adapted to numbers of persons under natural conditions.

Samples of children[78] from farms, villages and cities in regions of Ohio were examined through psychological tests designed to reveal degrees of mental health. The indices for farms and villages were better than for cities, thereby testing and supporting the observed greater admission rates to mental hospitals from city than country. The method is suggestively applicable in identifying populations susceptible to a particular mental disorder, including suicide.

Different personality patterns are observed in various disease processes. That of multiple sclerosis differs from poliomyelitis and Parkinsonism[30], and Kolb[60] has shown more mental deterioration and psychotic behavior in patients with multiple sclerosis than in a general population. The unanswered question is whether the origin is in differences in basic psychic constitution determining selection of those in a population likely to develop the disease, or whether organic changes associated with the disease itself are responsible.

Physical Constitution. No observations have been made on the relative frequency of suicide according to physical constitution as distinguished by Draper[24], or the genotypes of Sheldon[120]; and only to a limited extent for mental diseases generally[61].

Differences as outspoken as 14 times more angina and coronary disease in general populations than among mental patients, and 3 times more peptic ulcer suggest fundamental differences in physical constitution[41] between the 2 groups, in addition to the evident dissimilarity of environment.

In somatic as distinguished from psychic disease, nutrition has been many times demonstrated to have an effect on physical state and likelihood to disease. Nutrition surveys currently have this as their principal interest,

rather than the search for specific nutritional deficiencies. A possible relationship of nutritional state to frequency of mental disorder has scarcely been considered, even to the extent of testing for the simple correlation. Field trials have been directed towards a relationship between specific nutrients and academic performance[88a,b,47] of school children, but with equivocal results.

The present field surveys for chronic disease conceivably could incorporate selected mental illnesses, preferably those recognizable through simple criteria not requiring trained psychiatric skills. The purpose would be more than an improved census of the chronic ills of a community. Simultaneously collected data with uniform controls would promote knowledge of dual occurrence and of association between mental and physical illness.

Acquired Resistance and Susceptibility. An immunological contribution to acquired resistance does not hold in mass mental disease, other than for those few conditions caused by an infectious agent. However, acquired susceptibility is from a variety of sources. One of the more pertinent and commonly neglected in all mass disease, including the infections, is the effect of one disease in lowering resistance to another. The classical association of diabetes and pyogenic infection is in point. The evidence in relation to suicide is scanty. Stearns[123] found 15% of persons in his series of 160 suicides to have severe organic disease, principally neoplastic, heart and pulmonary. The relationship has not been explored for many mass mental illnesses.

Heredity. Most observations on hereditary factors in suicide are based on such instances as a history of suicide in an Illinois family[119] during 3 generations among 32 family members. Proof is by no means definite since environment is also similar in family groups.

Certain major mental diseases have a well established hereditary basis, notably schizophrenia[55]. To the extent that they relate to suicide, they also effect that condition. In a direct approach to hereditary factors in suicide Kallman and Anastasio[56], used the ideal material provided by twins, drawing on their file from New York institutions of some 2,500 twin index cases. Their observations, combined with other reported cases, mainly those of Loewenberg[74], gave the conclusion that suicide of itself has no genetic factor. Suicide involves such a complex combination of motivational factors as to render duplication of this unusual constellation unlikely, even in individual twin partners who show the same kind of psychosis.

Agents of Disease. Suicide falls into that class of causal complex where no single known factor is regularly present. It differs from most other mental disorder in that some tangible agent is usually identifiable, but with much variation from case to case. Poisons and bullets, knives and ropes are the direct agents, the *sine qua non* of the suicidal act (Fig. 4); and variously are of physical, chemical and biological nature.

The multiplicity of recognizable agents in suicide has a counterpart in such clinical entities among infectious diseases as puerperal sepsis and pneumonia. Of themselves and as a group, they resemble that other collection of agents which act in accidental traumatic injury[38b]. Recognition of an agent carries no implication that it is the sole determining factor, nor the most important, any more than in tuberculosis or malaria. In suicide indeed, the agent is usually of minor

consideration among recognizable factors determining the end result.

Certain patterns in suicide are closely related to the agent. Wide distribution in the environment, comparable to a high "community dose" of an infectious agent, is a common determinant of the kind of suicide. Suicide by firearms accounts for 40% of suicides among males in the United States,

Variations of agent pattern aid also in defining the biologic gradient of suicide, for Moore[83b] shows that ingestion of iodine is more common among those attempting suicide to attract attention, than for persons actually intending to end life.

Environmental Factors. A practical pattern for orderly arrangement of environmental factors in disease cau-

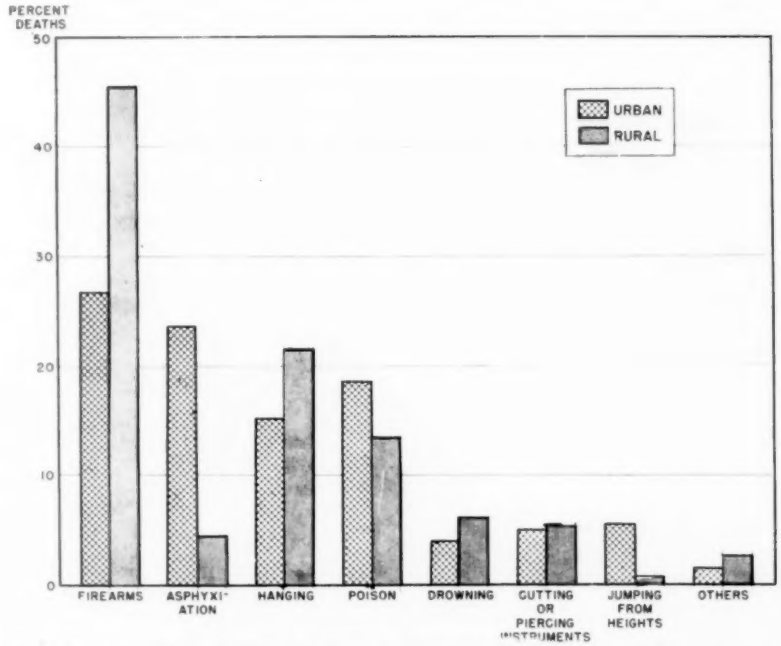

Fig. 4.—Suicide in Rural and Urban Areas, Percent of Deaths by Means Employed, U. S. Registration States, 1929. Source: Mortality Statistics, Washington Dept. of Commerce, Bureau of the Census, 1929.

while in Denmark[30] where guns are scarce, only 2% are by that means.

Sociologic and psychologic factors also enter into the choice of agent, in that women tend to prefer the more passive means of poison. The increase by a half and within a generation of the use by women of the more violent acts, such as shooting and hanging[80b], is more evidence of the altered social status of women.

sation[39] recognizes 3 divisions. They are the physical environment; the biological environment to include all other living things than man himself and the infectious agents as arbitrarily separated; and finally those features of the environment arising through association of man with his fellow man, the social environment.

Physical Environment. Year in and year out, a seasonal spring peak is a

consistent feature of suicide, observed since good statistics were kept in Europe[44] and in this country. Dahlgren[18] attributes this to the greater frequency with which manic depressive psychosis occurs in the spring. The phenomenon appears to be truly seasonal, since in Australia the greatest frequency is in January and February[136], while in the United States it is in May and June[123]. Most studies indicate the peak for attempted suicide is about the same as that for suicide, namely in the months of April, May and June.

Durkheim[26] tabulated 6,587 suicides by day of the week and found Monday and Tuesday had the highest rates, and Saturday and Sunday the lowest. Most suicides in the United States Army during the recent war occurred from 5 a.m. to 9.00 a.m. Durkheim[26] found the highest rates in a civilian population from mid-morning to mid-afternoon, a corresponding time after arising.

Suicide rates are thus seen to be highest early in a new year, a new week and a new day. Whereas spring is the beginning of a new year—biologically a renewal of life—and daylight is the natural beginning of a day, the beginning of a week is a man made arrangement and not the start of a natural cycle. This distinction has not been well observed in the literature on suicide. The suggestion follows that the principal motivation is social and psychological, rather than physical or biological.

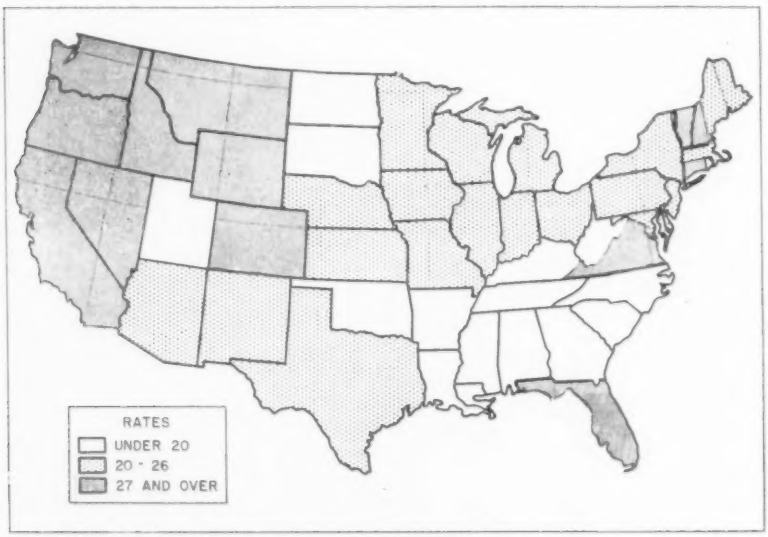

FIG. 5.—Suicide Rates Per 100,000 Population, White Male, by States, United States, 1940. Source: Data from Vital Statistics of the United States, 1940, (Department of Commerce, Bureau of the Census).

The geographical distribution of suicide in the United States (Fig. 5) shows a preponderance in the far west, notable exceptions being the elevated rates that characterize Virginia, Florida and some of the New England states. The variations are believed real

since artificialities introduced through varying practice in allocating causes of death scarcely enter into suicide. The relative regularity of the pattern also supports that view.

The higher rates in the far west have been explained[81] on the basis of the bad weather that characterizes those regions, an explanation offered by many since Morselli[84] first blamed suicide on cold gloomy climates. By partial correlations in respect to Negro populations, foreign born, average amounts of sunshine and mean annual temperature, Miner[82] proved that when elements of the social environment were held constant, the physical environmental correlations with suicide became insignificant.

Since 1900, cities in this country have had about half as much suicide as rural areas[25]. Hoffman has shown that the larger the city the higher the rate[50]. In her ecologic study of suicide in Chicago, Cavan[8] further showed the extreme rates to be in the downtown areas where lodging houses are concentrated and a shifting and unemployed population is characteristic. A similar pattern holds for schizophrenia and other mental disorder in Cleveland and St. Louis[100].

The observed differences in frequency of suicide according to time and place are in better definition of the suicide problems, but scarcely explain it. The causes are more likely resident in the social environment and in psychologic motivations of people.

Biological Environment. The biological environment is of outstanding importance in infectious diseases of animal origin and of arthroped transmission. Other than for relationships to food supply, it has little demonstrable place in causation of mental disease.

Social Environment. Environment is that setting of circumstances and conditions in which persons live and carry on their activities, the aggregate of all the external conditions affecting the life and development of an organism. The social component of environment is distinguished from the two other main divisions, physical and biological, as that part which deals with the association of man with his fellow man and with the products and ideas resulting from that association. The interaction between persons[9] that follows as a feature of association is marked by the existence of values, beliefs, intellectual products and attitudes, widely interpreted as influencing the behavior of groups from families to the universe of man[58,93]. The material products and processes specifically defined as technologies are of equal consideration. Buildings, roads, manufactured objects and domesticated plants and animals act in determining welfare and behavior and also in health and disease. Together these intellectual and material products of interaction form an interconnected whole, the social system, perhaps less precisely delimited than the physiological system of man but nevertheless a system of interrelated parts. Henderson[49] has pointed out the similarity of the two, that an outside pressure on a social system, such as a flood, if not too severe, temporarily disturbs the functioning of the system. When the force is withdrawn, the system resumes functioning essentially as before.

Primarily, a social system is a group of persons interacting only among themselves to the exclusion of all others. In times past and among isolated primitive groups[103] this condition was approximated but probably never attained, any more than our solar system is isolated from all others. Presently and on a large scale, Russia and her satellites are attempting such a closed system within their iron curtain.

In a primitive social system the range of contacts from family and friends through economic and political to religious contacts is restricted, sometimes to a few hundred persons. Within a small area, and given a long period of time, interactions tend to be repetitive and frequent. The resulting material products or technologies, and also beliefs and values, tend to be similar. Conversely, masses of persons occupying a larger space over limited periods, for example the United States[90,91,130] or the Middle East[105] since World War II tend to break up into sub-systems, interacting among themselves with the result that both intellectual and material products of the association tend to be less similar. Differences in beliefs and values are related to schisms and conflicts that are difficult to reconcile, as in labor and management. There is general belief and no small amount of proof that the increase during the past century in emotional disorders and less clearly in mental disease is related to these sources.

The purpose now is to identify those qualities of the social environment associated with high and low rates of suicide. No systematic categorization of the social environment is attempted, but rather a selection of those features that have been correlated with suicide. The result should be the beginning of a pattern for action by epidemiologists in relating causes of emotional disturbance and of mental disease generally to the social environment.

Constituent Groups. The social system of a governmental state or region[104c] is the usual point of departure in epidemiologic analysis. The social scientist distinguishes constituent sub-groups as territorial to include cities, tribes, suburbs, villages, or neighborhoods[21,104b,75]; various organizational groups such as political, business and religious[10a,107,104a]; and finally small face-to-face groups as of families or groups of friends[51,106]. Suicide has been related to a number of them.

Historians report little suicide in the cities and towns of the Middle Ages. Since the Reformation[25] an increasing frequency has been reported in all civilized countries. Zilboorg[133] holds the opposite view, that suicide is just as frequent among primitive tribes as in Western Europe and the United States today. Factual data are lacking.

Of organizational groups, suicide rates are generally less among Catholics than non-Catholics; for Catholic Eire 3.3 per 100,000, and 14.5 for Protestant Sweden for the years 1926 to 1930[25]. In Germany the lowest rates are seen in Catholic Bavaria. Italy[84] provides an especially good illustration, with low rates in Sicily and high rates in North Italy.

Regarding small face-to-face groups, the classical studies of Durkheim[26] and Halbwachs[44] have shown the connection between family status and the likelihood of suicide. For example, rates are greater for the widowed than the married, for single persons than for married, and greatest for the divorced[84]. Each additional child[44] adds an increment of protection. The positive correlation of suicide and numbers of boarding houses in various Chicago areas[8], was interpreted as the resulting break-up of face-to-face groups, those of family, friendship, and work.

Population Pressures. Rates for suicide have a relationship to the density and crowding of populations. Rural rates were long more favorable than those for cities[32], although the changing social structure tends to bring them closer to approximation. In large cities rates for suicide decrease regularly from the crowded central sections of cities[8] to the suburbs. Comparison of countries such as India and Japan with

sparsely settled Canada is less definite[25] because of lack of equally dependable data, and by reason of multiple cultural differences.

Circulation. The movements of people in respect to a universe selected for study involve 2 considerations, the number who move in and out of the prescribed population, and the movement of persons within the group. Immigrants[25,89] to other countries commonly have higher rates for suicide and for mental disorder generally than do people of the countries from which they come or the countries to which they go. The reasons are not always easily recognized. The kind of person who immigrates and resulting emotional reactions to the new environment require equal consideration.

The social implications of circulation within a group are less well defined in relation to mental disorder. Movement and circulation of industrial workers change during strikes, lay-off periods and depressions with a resultant effect on emotional disturbance[121]. Any relation to suicide is unknown.

Occupation and Other Roles and Statuses. Well marked differences can be demonstrated in frequency of suicide according to principal occupation. Physicians[102] for instance have suicide rates twice as great as for the white male population. Business men, professional and white collar workers[25] are more prone to suicide than artisans and laborers.

What a person does within a social framework has broader connotations than the mere nature of his gainful employment. Those individuals within a trade called upon to assume leadership of group activities or to act as foremen, often are subjected to stress for which they are ill prepared either by training or experience. Leadership has an individual hazard as evidenced by the appreciably greater suicide rates for officers[127] than for enlisted men in military practice.

Suicide becomes far more frequent among business men in time of depression than during normal business activities. Financial failure is reflected as well in loss of role and status in the community.

Activities. The kind of activities[51,76] strongly determine social environment. A group pursuing a normal vocation during peace time is subjected to stress of wholly another order than is an infantry platoon at the front in time of war[42]. Psychoneuroses are more frequent while suicide is less.

Cultural Values. All societies have cultural values, beliefs, ideas and attitudes. As disembodied elements, they are elusive factors of the social environment with which to deal, whether expressed verbally or by the written word[10a]. Translated into activities or technologies they become more tangible. As such, they can be counted and measured and their relationship to disease determined.

More than most other mass disease and mass injury, suicide contributes evidence to the opinion held by many social scientists that cultural values are a part of causal complex. Hara kiri of Japan and suttee once practiced in India[25] are instances of culturally prescribed norms leading to suicide in response to a social crisis. Halliday[45a] has analyzed the effect of changing attitudes in the upbringing of children during the past 100 years, as they reflect on mental as well as physical health. Experience suggests a broad contribution to many other mental and emotional disturbances, and to somatic disease as well. The drinking of wine in Latin countries and of tea in China are preventive measures arising from well founded belief in existing or one-time contamination of water supplies.

Verbal statement in expression of attitude and belief is a hard commodity to measure and often misleading. But difficult or not, what people say is an important means by which to learn about social environment. The skilled investigator comes to separate reality from fantasy, acquiring information that is valuable in itself and also as a guide in acquiring facts by direct observation.

TECHNOLOGICAL DEVELOPMENTS. Provisions for medical care, for public health and preventive medicine, the modern schools and the automobile are technological developments of modern human societies with demonstrable effect on disease incidence. Public health agencies and medical technology have brought communicable disease as a cause of death to a secondary position in relation to degenerative and neoplastic diseases. The automobile introduced in 1910 a wholly new factor in death and disability from trauma.

Technological developments[106,16,108] are features of the social environment that can be measured and counted. The relation to health and disease is determined sometimes directly and sometimes by indirect means. Morselli[84] in 1875 used the number of miles of railroad to judge technological development in relation to mental disorder and suicide. The use of illuminating and other gases and the production of new chemical compounds in medicine have affected the agent pattern in suicide. Few factual data are available on those evident influences of technology that arise through strain and stress associated with a mechanized age. Industrial medicine has developed into an important component of medical practice, but with more attention to the effect of industry and technology on physical than mental ills.

ANALYSIS OF A SOCIAL FACTOR. The social factors just described are fairly abstract and complex concepts. They lack the concrete nature that antibodies have as a means to measure resistance or susceptibility to infection. When a positive correlation is demonstrated between high rates of suicide and one general group of social factors, the work of the social scientist has just begun.

These factors are not simple social elements manipulated statistically to aim at a contribution to causation, but are complex compounds requiring careful dissection; only so are the specific elements to be identified as they relate to suicide or any other condition, mental or physical. The situation marks a common ground between biologist and social scientist. Each faces the problems of analysis and measurement of significance. In the example cited above, specific immunity is likewise not the whole of resistance to infection.

The broad factors of causation differ materially in the 2 fields of biology and the social sciences. In both circumstances some are more definite than others. Some can be measured directly and some only indirectly. The identification of groups of variables and their separation bring into play the specialized techniques of each discipline. The fundamental method is essentially the same as illustrated by the information on suicide and constituent groups.

Towards the end of the 19th century Morselli had demonstrated suicide rates to be higher in northern than in southern Europe. One explanation was the gloomy climate. Later Durkheim reasoned that climate was not the critical factor but that the population in north and south was on the one hand Protestant and the other Catholic. With added information on industrialization and family composition he came

to the conclusion that persons who cease to be members of groups and become detached from their fellow man are more prone to suicide. This he called "exaggerated individuation." Sainbury[70] in a recent study in London has correlated suicide with persons living alone in private homes (Fig. 6). Explanation of the concept of constituent groups thus led to recognition of the particular critical element as something that approximates isolation. The way from gloomy climate was long. In further refinement, investigation turns now to direct study of the kind and number of human contacts of persons who commit suicide, in the attempt to come still closer to the critical variables in suicide as they occur under at least one set of circumstances.

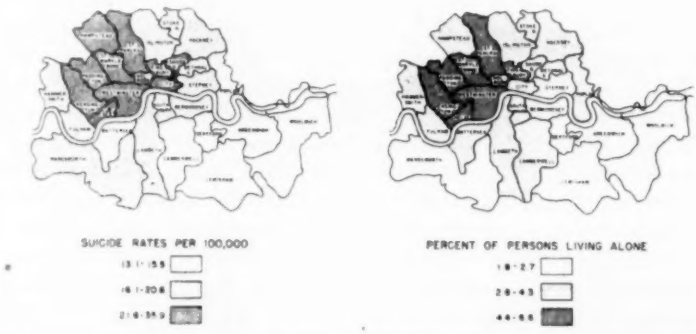

FIG. 6.—Suicide and Isolation, London, 1929-1933. Source: Data of Sainsbury (70).

Mowrer[85] has offered evidence that many psychoses, juvenile delinquency, adult crime, suicide, alcoholism, drug addiction, family disorganization and the like all have highest rates in and around the loop section of Chicago. The social stress associated with this slum boarding house district acts in a variety of ways. One interpretation is that all these disturbances are symptoms of the specific stress. A more reasonable conclusion is that the stress gives a result in varied form dependent upon host factor. The situation is in clear analogy with hemolytic streptococci as they lead to tonsilitis, puerperal sepsis, scarlet fever and abscess formation.

An identified social stress may be the guide to presumably existing disease; existing disease may be the point of departure in search of cause resident in stress. The principle is the same as that for biological factors, for example mosquitoes and malaria.

Methodology in Mass Mental Disease. The epidemiologic method is judged to be a reasonable part of medical effort in mental and emotional illness, as in other community disease. A definition of the limits and content of the epidemiological field was presented as the first requisite to a more productive approach. That depends chiefly on better clinical description and classification of disease entities.

A scheme was then presented for epidemiological analysis of a single mental illness. It gave weight to both biological and social sciences. It evolved from a concept of host, agent and environment as providing mutual contributions to origin, with causation consequently multifactorial. Time and place are governing factors over all three components of the causal com-

plex. Mutual and reciprocal interaction takes place between all three and between individual constituents of each. Age and sex are thus biological characteristics of the host and also features of the social environment. Geography is a factor of both the physical and the social environment.

The epidemiologist, reasoning from an experience in mass manifestations of a variety of diseases and injury and appreciating both social and biological influences on mass disease behavior, views questioningly some current attitudes on origin of mental illness. Mental disorders do not permit generalization that they arise from experiences and improper reaction to experiences. Some clearly are not of that source. The scientific postulate of a hundred years ago, that an understanding of brain structure is essential to an understanding of human behavior[37] is not to be lost in the enthusiasm for psychogenic origin. An origin of mental disease based on pathologic physiology would seem to have as much promise as does interpretation of psychologic events in eventual development of the precise diagnostic tests so needed in clinical and epidemiological studies. The social scientist or psychologist who discounts biological factors in disease suffers the same difficulties as the biologist who views a morbid process as wholly the function of an infectious agent, to the neglect of social contributions to causation. Opportunities for an inter-disciplinary approach are evident in a number of directions.

Social stress is appreciated[42] as an important determinant of mental disorder. The nature and content of social stress needs better definition. Leighton[64] has initiated studies to measure this factor. Selecting factors presumably associated with high and low stress, their presence in a population is determined through direct field study and then correlated with the frequency of mental disorder. A consideration of concomitant physical illness gives additional useful information. The study of epidemics such as that of hysteria in a Louisiana high school[114] is another sort of approach.

A recent mission to Israel gave opportunity to observe (Gordon) a situation in nature permitting test of the existing hypothesis that some emotional disturbances of adult life have their origin in deprivation experiences of infancy. Kibbutzim are communal agricultural settlements in which children are separated from parents practically from birth, and are brought up by professional workers. Parents visit at daily or longer intervals. From birth, children of both sexes live, work, study, sleep and play with others of their own age. Age groups merge as they grow older, the size of groups being determined by that of the Kibbutz and the ages of the children. A characteristic of the system is that attendants progressively delegate authority to these groups so that norms and discipline are largely determined by the group. A psychiatrist of that country has compared emotional problems of other children, largely urban and living in their own families, with those of children of the Kibbutz. Dr. B. Kaplan in a personal communication observed that in infancy and early childhood the emotional adjustment of the Kibbutzim children was less satisfactory but by adolescence was better than that of children reared in the usual Israeli family. As adults, those of the Kibbutz system have a more stable emotional life as judged by interpersonal relations. During the Arab-Jewish war, young people of Kibbutzim tended to manifest fewer battle neuroses than other groups, although commonly fighting as shock troops. Differences in the incidence of

psychoses between the Kibbutzim group and persons reared in a family environment have not been observed. The information cited suggests the promising results to be had through longitudinal field study.

An epidemiology of mental disorder requires an adaptation of classical procedure to give greater emphasis on social techniques. New skills are required, particularly the field methods of the anthropologist and those of the social scientist. Cooperation in clinical and epidemiological endeavor is apparently of the first order.

Clinical Aspects. Until a valid basis for classification can be generally employed, data from different areas can not be properly compared. Diagnosis at a descriptive level is not enough. Tidying up that deficiency is the business of clinical psychiatry.

A second consideration is that the current concept of many mental disorders has been determined through study of patients with clinically evident illness. Knowledge of pre-morbid personality difficulties is immature. The opportunity to acquire that information seemingly depends on psychiatrists going into the field to conduct observations on the sick and the well as a part of an epidemiological team. The method has served with other diseases.

Experimental Aspects. The dominant part of laboratory experiment in study of causation has had earlier emphasis. The epidemiologist must be prepared for the field trial of diagnostic procedures or newly recognized agents of disease as they come to be defined. His methods are both suitable and essential.

Experimental epidemiology is observation of groups of animals under controlled conditions[131] to determine mass behavior of disease. Studies of this general nature, employing social and biological methods, give promising leads on behavior reactions of groups of dogs[36,118], mice[116a,b] and others[117, 124,109].

Field Epidemiology. Direct observation of events as they occur in nature is the fundamental basis of field investigation. This is the participant observation of the anthropologist, long practiced in epidemiology as "shoe leather epidemiology." It involves living and working in the universe studied[115]. It is to be distinguished from statistical analysis of assembled records made by others. The technical procedure of field surveys gained through experience with other mass disease presumably holds for mental disorders. A preceding systematic design of study is equally essential to eliminate difficulties in analysis. Field procedure is directed toward distinguishing those factors of host and environment present in the disease under observation from those existing in its absence.

Small Group Epidemiology. Small group studies of selected atypical instances of mental disease depend primarily upon the comprehensive observations by which the atypical is recognized. The procedure then is to study such exceptions[6] as persons of high income and high prestige who are alcoholics, the manic depressive psychotic from the slums and the schizophrenic from the suburbs. Observation of such precisely timed events as psychotic manifestations associated with adenoma of the pancreas or postpartum psychosis provides opportunity to demonstrate causative factors generally operating but ill defined.

International Activities. Field study of disease is sometimes directed toward observation of one disease in its broader distributions, even global, and sometimes toward investigation within a prescribed area of all disease of a class. The international view of mass mani-

festations of mental disorder, little touched upon, would seem to have material advantage if for no other reason than the demonstrated social influences so variable from culture to culture. The epidemiology of most mental diseases is presumably different in the United States from that in India, Syria, or Peru.

A disease is known through information of its variations as well as through knowledge of its usual behavior. General paresis commonly shows an inverse correlation with economic status. In Germany it was long taught that the greater incidence among intellectual classes existed by reason of greater mental stress and strain. Expanding information showed that the incidence varied from country to country and at different times, although the reasons are not yet identified.

The advantages which accrue to study of organic disease in simple cultural situations[87] would appear especially applicable to mental disease. Principle is often easier to define, with the results later applied to more complicated civilizations.

Organization for Epidemiological Investigation. Epidemiological methods are used by physicians, health officers, statisticians, demographers, anthropologists, sociologists and many other professional workers in mental and other diseases. A superior result often follows cross-cultural participation, where workers from the different fields combine efforts in a team endeavor. Field study in mental disorder is clearly not a function of any single discipline, social or biological. Psychiatric direction is desirable because of accepted principle that a knowledge of the clinical disease is requisite to study of mass relationships. Promise of future accomplishment seemingly rests with those young psychiatrists having sufficient patience to acquire a command of epidemiological method and a knowledge of social relationships.

Secondary personnel for the work of the day become increasingly important as field studies extend to the scope now practiced. Medical students have been used[53a] as field investigators. In special situations the psychiatric social worker has a part for which there is no substitute. The epidemiologist tends to place first reliance on that assistant of repeatedly proven capacity, the public health nurse. To visit homes on errands as difficult as these, requires skill and experience. A woman has many advantages, and this particular lady has tackled jobs from accidents to juvenile delinquency, and all in her stride.

Objectives. The form of epidemiologic method combining social and biological disciplines, here presented, suggests no remarkable contribution to a definitive etiology of mental disease. Most assuredly it can identify disease situations in communities. To recognize a characteristic of a disease is a clear gain, for instance the niceties of age of attack. Intelligent search for causes by all available method is thereby facilitated. Progress is marked "not so much by the problems we are able to solve as by the questions we are enabled to ask."

A more general application of epidemiologic methods to mental disorder should lead to a better understanding of these diseases if for no other reason than that stated by McLeod, that "as soon as we require to make measurements we feel again and again compelled to replace approximations by exact definitions."

The purpose of epidemiology as the diagnostic discipline of mass disease[38c], is to show the direction of an intelligent public health practice. It has so functioned in mental disorder. In mili-

tary practice of the last war[1b], an analysis of trends and variations in incidence gave presumptive indices of special stress in given military units and geographical areas. Conversely, identification of units or areas with stress situations was a guide in search of excess prevalence of mental disorder. Industrial medicine has made a start with similar methods in business and industry.

Summary. A pattern of epidemiologic analysis, based on suicide as a mass phenomenon and combining techniques of the social and biological sciences, is presented as a means for investigation of mental and emotional disorders as mass manifestations of populations.

The development of epidemiological method has been principally along biological lines. The evidence suggests that emotional disorder as a mass phenomenon can not be understood without the aid and participation of the social sciences. The social disciplines have contributed to medicine, although interest in disease has been secondary. The epidemiologist, through increased familiarity with social sciences, can expect to profit materially in the particular field of mental and emotional disorder, and also in work with mass disease.

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BOOK REVIEWS AND NOTICES

GLOBAL EPIDEMIOLOGY. A GEOGRAPHY OF DISEASE AND SANITATION. BY JAMES STEVENS SIMMONS, M.D., Ph.D., Dr. P.H., Sc.D. (Hon.), Dean and Prof. of Pub. Health, Harvard Univ. Sch. of Pub. Health; Tom F. Whayne, M.D., M.P.H., Dr. P.H., Chief, Prevent. Med. Div., Office of Surg. Gen., U. S. Army; Gaylord W. Anderson, M.D., Dr. P.H., Mayo Professor and Director, Sch. of Pub. Health, Univ. of Minn.; and Others. Vol. 2, Pp. 652; ills. Phila.: J. B. Lippincott Co., 1951. Price, $15.00.

THE first volume of *Global Epidemiology*, which deals with the distribution of disease and the status of public health in all parts of the world, was published 7 years ago and covered India, the Far East, and the Pacific Area. The present volume, which covers Africa and the adjacent islands, not only deals with local health administration, medical facilities, environmental sanitation and disease problems, but includes discussions on the racial, social, and economic factors influencing the health status of the peoples concerned.

Like the first volume, it makes available to students of world health some of the vast amount of information accumulated by the Medical Intelligence Division of the Preventive Medicine Service of the Office of the Surgeon General of the U. S. Army, which has broadened as public health has become increasingly international in scope to include areas little known before World War II. As in the first volume, the authors have assembled a great deal of extremely valuable data of assistance, not only to professional workers in the fields of medicine and public health, but also to the agencies working toward world understanding and international co-operation.

J. K.

MENTAL HEALTH AND THE PREVENTION OF NEUROSIS. By JOACHIM FLESCHER, M.D., Asst. Clin. Director, Child Guidance Inst., Jewish Board of Guardians, New York City. Pp. 605. New York: Liveright, 1951. Price, $5.95.

THIS book lives up to its title, since it deals very completely with the subject of mental health, and it should make a contribution toward the prevention of neurosis. The style is a fine combination of the scientific and the human. The author begins with the instincts and environment in childhood and in this section of the book he keeps always before the reader a good balance between these forces.

To quote: "Too often, unfortunately, parental concern over his future constitutes the only motive for the education given the child. Their preoccupation with the 'end result' renders them harsh and insensitive to the immediate developmental needs of their offspring. . . . The 'dosage of reality'—the amount of renunciation required of the child—must obviously be carefully timed in relation to his given developmental phase. But in order to formulate principles on when to indulge and when to be firm, when to satisfy and when to frustrate, we must first look at the child's impulses, wishes and inclinations, and the ways in which they evolve from basic human instinctual drives. Thus, we shall know how to avoid granting satisfaction when, in view of the child's psychological strength, renunciation could be safely required, or enforcing sacrifice when this cannot fail to have a traumatic effect."

The second part of the book deals with normal, psycho-instinctual development, a well-arranged discussion of personality growth. In the third part, abnormal development and psycho-instinctual disorders are taken up. A discussion of the neuroses and character disorders is included, with one chapter on psychosis and the aggressive drives.

The fourth part deals with the principles of psychic help. This takes up such things as the parental influences on the child and social and cultural strivings, and discusses the role of religion and the place of the family.

The fifth part deals with the practical prevention of neuroses in which the handling of some of the critical stages of development are discussed to show the kind of desirable parental attitudes which should prevent neurosis. There are excellent suggestions here for parent and teacher, and the last two parts of the book distinguish it from other books which have stressed causes and symptomatology but have been short on positive recommendations. This book should definitely fill a place in the modern literature on mental health and is also recommended for the parent, teacher, clergyman, and anyone working actively with the young in the process of development. O. E.

DIE NERVENKRANKHEITEN. BY Prof., Dr. GEORGES SCHALTENBRAND, Med. Director, Univ. Neurolog. Clinic of Würzburg. Pp. 880. 539 illus. Stuttgart, Germany: Georg. Thieme-Verlag, 1951. Price, DM 87.00 (about $20.70).

THE author has attempted a book which will bridge the gap between the technical treatises in neurology and the small com-

pends on this subject. He offers the present volume as a first of 2 parts of a treatise on neurology.

The book is entirely in German and consists of 25 chapters. The profuse illustrations include gross specimens, microscopy of tissues, charts, tables, schematic drawings, photographs of patients, and some excellent photographs of tumors exposed at craniotomy. Each subject is elaborated as follows: 1) short historical note; 2) pathological anatomy; 3) clinical progress; 4) differential diagnosis; 5) treatment and prognosis.

Many subjects are thus described with no more than a page of text. The bibliography appears to be very comprehensive and thorough; however, there is only an occasional reference to articles published after 1945.

This book is recommended for medical students and the general practitioner who have knowledge of German. M. S.

CONGENITAL DISLOCATION OF THE HIP. By JULIUS HAAS, Consulting Orthopedist, Montiefiore Hospital, New York City. Pp. 405; 174 ills. Springfield, Illinois: Charles C Thomas, 1951. Price, $12.50.

THIS timely monograph can be considered excellent, a fact not surprising since the author, after years of association with Lorenz, succeeded him at the Orthopedic Young clinic of Vienna, and thus has had ample opportunity to record observations of his specialty. The work is based on more than 2,000 cases of this common congenital deformity. It is obvious that a text of this size and type is, of necessity, comprehensive. As such, it is recommended for those especially interested in orthopedics and orthopedic surgery. A. S.

TEXTBOOK OF PSYCHIATRY. By EUGENE BLEULER, M.D. Translated by A. A. BRILL. New York: Dover Publications, Inc., 1951. Pp. 635; 51 ills. Price, $7.50.

THIS book is a reissue of Dr. Bleuler's original work first published in 1916 and translated into English by Dr. A. A. Brill. It is a well written, comprehensive book which departed from the then prevalent Kraeplinian tendency to classification. It includes much of the thinking of psychoanalysis but is by no means a strictly psychoanalytic textbook. There is a wealth of material in the book which is really comprehensive in its scope.

Of greatest importance is the understandable method of presentation of psychopathology as well as the various individual mental and emotional disorders. Obviously certain portions are outmoded, particularly in regard to newer treatment procedures in both functional and organic psychoses. Yet this is a book which should be in the library of every serious student of psychiatry and should prove useful to any physician who has occasion to see patients suffering from psychiatric disorders. S. F.

BIOCHEMISTRY AND PHYSIOLOGY OF PROTOZOA. Volume I. Edited by ANDRE LWOFF, Head of Dept. of Microbial Physiol., Pasteur Inst., Paris, France. Pp. 434; 34 ills. New York: Academic Press, Inc., 1951. Price, $8.00.

THE first volume is a series of contributions dealing with the nutrition, metabolism, and growth of the Phytoflagellates, the parasitic flagellates and Amebae, the Trypanosomidae and the Bodonidae, the biochemistry of ciliates, and also the biochemistry of Plasmodium and the influence of antimalarials. In this monograph the attempt by the editor to collect under one cover the noteworthy contributions upon this subject is commendable and will prove of great value to those engaged in research microbiology and allied subjects. W. T.

SCOLIOSIS. PATHOLOGY, ETIOLOGY, AND TREATMENT. By SAMUEL KLEINBERG, Lecturer in Orthopaedics, New York Univ. Med. Sch. Pp. 286; 163 ills. Baltimore: Williams & Wilkins, 1951. Price, $7.50.

THIS study of scoliosis, including the pathology, etiology, and treatment, supplies further insight into a complex disease which until the present time has been highly resistant to successful treatment.

This resistance to treatment is mainly due to the lack of basic knowledge of the cause of the disorder, and this Author attempts to shed more light, and also to open up more avenues of thought, on the etiologic factors by putting into one volume the anatomy, embryology, and physiology of the scoliotic spine. He then attempts a classification and discusses the pathology from the standpoint not only of the skeletal structures involved, but also of the changes present in the visceral structures.

Treatment includes gymnastic exercises, forcible correction, and surgery, with mention of some of the recent experimental surgical trends.

As is true with all texts on disorders with obscure etiology, many questions regarding scoliosis are left unanswered.

However, this book is a very welcome addition to the literature on the subject and it is gratifying to feel that the author has taken a step forward in the solution of a very difficult problem. L. J.

POST-GRADUATE LECTURES ON ORTHOPEDIC DIAGNOSIS AND INDICATIONS, Vol. 2. By ARTHUR STEINDLER, M.D., F.A.C.S., Prof. of Orth. Surg., State Univ. of Iowa. Pp. 208; 209 ills. Springfield, Illinois: Charles C Thomas, 1951. Price, $6.00.

THIS text presents 2 groups of lectures. The first group is divided into 5 lectures on paralytic disabilities and the second group is divided into 5 lectures on static disabilities. The Author presents in a brief and concise manner the etiology, pathology, and treatment of practically every paralytic disorder and static disability of interest to the orthopedist. The section on low back pain is of value to the practising orthopedist.

The one objection that comes to mind is that in an attempt to cover a vast amount of material in a small amount of space, the Author has had to be quite brief in discussing many of the subjects. It would seem that for the post-graduate group, more detail would be indicated. However, considering it as a rapid review of the paralytic and static disabilities, it is a valuable addition to the orthopedist's library. L. J.

PSYCHOANALYSIS, MAN AND SOCIETY. By the late PAUL SCHILDER, M.D., Ph.D. Arranged by LAURETTA BENDER, M.D. New York: W. W. Norton & Co., Inc., 1951. 1st ed. pp. 382.

THE material of this book which, as the title suggests, is sociological in nature, was being worked on by the author at the time of his death in 1940. It is a series of papers arranged posthumously by his wife, Lauretta Bender. The papers form a coherent whole and touch upon many subjects in 20 chapters. Among the subjects covered are: Psychoanalysis and Philosophy, Social Neuroses, Success and Failure, A Study of Criminal Aggressiveness in Man, Remarks on the Psychology of War.

In his introduction Dr. Schilder indicates his preoccupation with the timeliest of problems when he says, ""Psychiatry must consider the problems of leadership and find out of what leadership consists, and progress from this problem to the psychological evaluation of where the leadership leads. The psychiatrist must re-evaluate the goals of the leader, must ask whether these goals can be approved and whether they will lead to the full development of personalities, the final goal, whether there is a catastrophe in the world or not.

"The psychiatrist must further study the ways in which insight into the worth-whileness of a goal can be imparted to others, and how these individuals can be protected from being swayed by propaganda which does not offer true goals, either in a general sense for the larger community or from the point of view of the individual personality."

Each paper is fresh, stimulating and readable. Many of them contain clinical case presentations. O. E.

ROENTGEN ANATOMY (In Spanish and English). By DAVID STEEL, M.D., St. John's Hosp. and Evangelical Deaconess Hosp., Cleveland. Pp. 109; 108 ills. Springfield, Illinois: Charles C Thomas, 1951. Price, $8.00.

THIS is an atlas of fundamental roentgen anatomy consisting of roentgenograms made in the commonly used positions with matching line drawings. The right hand pages show the roentgenograms, with the anatomic parts named in Spanish. The left hand pages diagram and name minutely and accurately in English the various structures and shadows visualized. The reproductions of the roentgenograms are good, with the exception of the skull and sinus projections, where finer detail would give them more value. This is a useful book for students of roentgenology. D. H.

THE ENZYMES. CHEMISTRY AND MECHANISM OF ACTION. Edited by JAMES B. SUMNER, Lab. of Enzyme Chem., Cornell Univ., and KARL MYRBÄCK, Instit. for Organic Chem. and Biochem., Univ. of Stockholm, Sweden. Vol. II, pt. 1. Pp. 790; ills. New York: Academic Press, 1951. Price, $14.80.

PARTS 1 and 2 of the first volume of this excellent reference work on enzymes were reviewed in this Journal (**221**, 474; **222**, 609, 1951). The first part of the second volume contains 21 chapters by 23 contributors who deal with the following enzymes or enzyme mechanisms: Theory of Oxidation-Reduction; Thermodynamics and Mechanism of the Phosphate Bond; Transphosphorylating Enzymes of Fermentation; Dephosphorylation of Adenosine Polyphosphates; Aldolase and Isomerase; Keto Acid Decarboxylases; Amino Acid Decarboxylases; Desulfinase; Codehydrogenases I and II and Apoenzymes; Succinic

Dehydrogenase; Hydrogenase and Hydrogenylase; Flavin-Containing Enzymes; The Iron-Containing Enzymes (A, Cytochromes; B, Catalases and Peroxidases, "Hydroperoxidases"; C, The Enzyme-Substrate Compounds and Mechanism of Action of the Hydroperoidases); Copper Oxidases; Oxidation of Amino Acids; Oxidation of Amines; Lipoxidase or Unsaturated-Fat Oxidase; Enzymes in Luminescence; Oxidation of Organic Sulfur; Anaerobic Glycolysis, Respiration, and the Pasteur Effect; Yeast and Mold Fermentations.

All of the chapters are written by recognized authorities in their special fields. Of particular interest to the Reviewer is the admirably complete account of the iron-containing enzymes (chapter 56, pp. 357-452). This chapter will serve to illustrate the general arrangement of the text throughout most of the volume. The first part deals with cytochromes, their chemical and their biological properties (by K. G. Paul); in the second part H. Theorell discusses the catalases and peroxidases ("hydroperoxidases"), their occurrence, action, purification, chemical and physico-chemical properties, and their physiological rôle. The concluding part of the chapter, written by Britton Chance, considers the enzyme-substrate compounds and the mechanism of action of the hydroperoxidases; the methods for their detection; the physical and chemical properties of the enzyme-substrate compounds, their equilibrium properties, their reaction kinetics, their general properties; and, finally, a summary of present-day knowledge and a discussion of future possibilities.

It is no overstatement that this up-to-date reference book on enzymes in the English language fills a need long felt by physicians, biologists, and chemists. B. L.

TEXTBOOK OF GENERAL PHYSIOLOGY. By HUGH DAWSON, D.SC. (Lond.), Scient. Staff, Medical Research Council. Pp. 659; 288 ills. Phila.: Blakiston, 1951. Price, $7.00.

THIS textbook constitutes a means whereby students, medical personnel, and research persons can easily approach the detailed basic general physiology or any field of special interest. The figures and tables are extremely well chosen to illustrate the points under consideration. The book contains a large quantity of useful fundamental information. Its chapters are nicely organized and the one dealing with the characteristics of excitable tissue is excellent. M. O.

SURGERY OF THE STOMACH AND DUODENUM. By CLAUDE E. WELCH, Assoc. Visit. Surgeon, Mass. Gen. Hosp.; Clin. Assoc. in Surg., Harvard Med. Sch. Pp. 349; 79 ills. Chicago: Year Book Publishers, 1951. Price, $8.50.

THIS little handbook of common surgical procedures of the stomach and duodenum is a concise, clear presentation with 79 accurate step by step diagrams including an unbiased brief description of technical safeguards and pitfalls not emphasized in many larger volumes, which may prevent errors and serious postoperative complications. For example, the author's multiple methods of handling the duodenal stump will benefit the surgical resident who is encountering these various complications. It is to be noted that all of the operative procedures presented are not widely accepted. Although, as the author states in his prefare, ". . . gastric surgery cannot be reduced to a summation of technical maneuvers . . .", this book is an excellent technical guide for surgeons who are endeavoring to follow the modern trends in surgery of the stomach and duodenum. O. L.

SYPHILIS. By RICHARD S. WEISS, M.D., and HERBERT L. JOSEPH, M.D. Pp. 180; 38 ills. New York: Thomas Nelson & Sons, 1951. Price, $5.00.

IT takes considerable courage these days for anyone to undertake the task of putting in writing what should be the facts regarding syphilis. It is even a greater task to put this information into a small space. In the span of 180 pages, Weiss and Joseph have compressed sufficient data to enable the general practitioner, the Armed Forces medical officers, and medical students to have a reliable guide.

On the whole this book is well written, has excellent photographs, bibliography of good articles, and a comprehensive index. The viewpoints are, generally speaking, conservative. In addition to having a penicillin schedule for therapy, the authors have wisely included a brief discussion of the older treatments for communities where penicillin is not yet in vogue. In general the composition is first class, but uniform adoption of the proper name for the organism presumed to cause syphilis would be helpful. This organism is variously called, usually correctly, either *Treponema pallidum* or *Spirocheta pallida*, but in many instances, incorrectly, *T. pallida*.

This is a minor matter which can be corrected in future editions.

The reviewer can appreciate the great task which these authors have performed in condensing into so short a space a good summary of present-day practice in syphilis. H. B.

SPEZIELLE PATHOLOGIE DER KRANKHEITEN DES ZENTRALEN UND PERIPHEREN NERVENSYSTEMS. By Prof. Dr. GERD PETERS, Univ. of Bonn, Germany. Pp. 437; 214 ills. Stuttgart: Georg Thieme–Verlag, 1951. Price, DM 56 (about $13.40).

DESPITE the considerable development of neuropathology in pre-war Germany, a monograph dealing with the special pathology of the nervous system has been lacking. This book attempts to fill the gap. It deals with inflammatory diseases, vascular reactions, senile changes, degenerative and atrophic processes, tumors and injuries. For the pediatrician, the chapters on the effect of fetal injuries will be of interest, and for the internist, the central changes induced by metabolic disorders, infectious diseases, and diseases of the blood, of the gastrointestinal system, and of the various glands, particularly the endocrines, are of value. A special chapter is devoted to the hypothalamus-pituitary syndrome. Except for minor defects, for example, the lack of illustrations of peripheral nerve injuries and of a chapter on the pathology of the vegetative ganglia, the book gives an excellent introduction to neuropathology. Very clear illustrations, showing chiefly specimens from the research institutes in Munich and in Berlin-Giessen, are helpful for understanding the text. E. S.

STATISTICS FOR MEDICAL STUDENTS AND INVESTIGATORS IN THE CLINICAL AND BIOLOGICAL SCIENCES. By F. J. MOORE, M.D., Assoc. Prof. of Exper. Med., Univ. of Calif. Sch. of Med.; F. B. CRAMER, B.A.; and R. G. KNOWLES, M.S. Pp. 113; 11 ills.; 8 appendix tables. Phila.: Blakiston, 1951. Price, $3.25.

As is indicated by the title, the authors have attempted to supply instruction for both medical students and medical investigators. There is a tremendous difference between these 2 classes of readers.

It is the Reviewer's opinion that beginning students in the art of healing do not need this much instruction in the advanced sciences of medical research. The book has been designed as a supplementary text to an extensive lecture and laboratory course. The time for such a course is available in few medical schools; therefore, the usefulness of the text to medical students is severely limited. It is to be hoped that these authors' treatment may result in future increases in the time allotted to teaching medical statistics.

On the other hand, this book will serve as only an introduction to the statistics needed by investigators in medical research. Included are descriptions of the Normal Curve of Error, this Curve being fitted with experimental data; tests for Significance; and a chapter on Experimental Design. The treatment of these subjects is too extensive for an uninitiated student, but it is sometimes inadequate for medical research.

The book is presented in typescript form. This renders its physical appearance unjustifiably unattractive. It may appear discouragingly difficult to first or second year medical students. R. P.

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